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Abbreviations and acronyms

3TC	lamivudine
ABC	abacavir
ALT	alanine aminotransferase
ARDS	acquired respiratory distress syndrome
ART	antiretroviral treatment
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
BID	twice daily
BUN	blood urea nitrogen
CK	creatine kinase
CMV	cytomegalovirus
CNS	central nervous system
CRP	C-reactive protein
CVD	cardiovascular disease
d4T	stavudine
ddI	didanosine
DOT	directly observed treatment
DRV	darunavir
EAP	expanded access programme
EFV	efavirenz
eGFR	estimated glomerular filtration rate (=creatinine clearance)
ELISA	enzyme-linked immunosorbent assay
ENF	enfurvitide
ETR	etravirine
FDC	fixed-dose combination
FPV	fosamprenavir
FTC	emtricitabine
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL-c	high-density lipoprotein cholesterol
HPV	human papillomavirus
HSR	hypersensitivity reaction
HSV	herpes simplex virus
IC50	50% inhibitory concentration
IDU	injecting drug user
IDV	indinavir
IgG	immunoglobulin G
IHR	ischaemic heart disease
INR	international normalized ratio
IRIS	immune reconstitution inflammatory syndrome
LDH	lactate dehydrogenase
LDL-c	low-density lipoprotein cholesterol
LFT	liver function test
LPV	lopinavir
NTM	non-tuberculosis Mycobacterium infection
MTCT	mother-to-child transmission
MRV	maraviroc
NFV	nelfinavir

NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NVP	nevirapine
OI	opportunistic infection
OST	opioid substitution therapy
PCP	Pneumocystis jirovecii pneumonia (formerly P. carinii pneumonia)
PCR	polymerase chain reaction
PEP	post-exposure chemoprophylaxis (medicine given after exposure)
PGL	persistent generalized lymphadenopathy
PI	protease inhibitor
PI/r	PI with low dose ritonavir to increase plasma concentration (booster)
PLHIV	people living with HIV (=HIV positive people)
PML	progressive multifocal leukoencephalopathy
PREP	pre-exposure chemoprophylaxis (medicine given before exposure)
QD	once daily
/r	ritonavir given as pharmacological booster
RAL	raltegravir
SQV	saquinavir
STI	sexually transmitted infection
TAM	thymidine analogue mutation
TC	total cholesterol
TDF	tenofovir
TDM	therapeutic drug monitoring
TG	triglyceride
TID	three times daily
TPV	tipranavir
TSH	thyroid-stimulating hormone
VDRL	venereal disease research laboratory
VL	viral load (number of viral copies in plasma)
ZDV	zidovudine (also known as azidothymidine (AZT))

Definitions for strength and quality of recommendations

Concepts relating to strength of recommendations for use of a given intervention

Strong	strong recommendation for the statement
Moderate	moderate recommendation for the statement
Optional	optional recommendation for the statement
No recommendation	no evidence to inform use of intervention

Concepts relating to quality of evidence guiding recommendations for use of interventions

A	data from reasonable powered randomized controlled trials using relevant endpoints
B	data only from well-designed prospective observational studies assessing clinical endpoints only
C	data from case stories and/or expert opinion only

When recommendations on choices between regimens are expressed, the following concepts are used

Preferred	regimens shown to have optimal and durable virological efficacy, and favourable tolerability
Alternative	regimens that are virologically effective but have potential disadvantages when compared to preferred regimens
Acceptable	regimens that are less well studied or are associated with impaired tolerability or efficacy compared to the preferred or alternative regimens

Acknowledgement

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The updated version of the protocol is built on new evidence in the area of HIV/AIDS treatment and the global WHO 2010 recommendations for a public health approach "Antiretroviral therapy for HIV Infection in Adults and Adolescents". The process included consultation with Regional clinical experts through a 2010 meeting in Kyiv (Ukraine) and electronic communication with them to ensure that the updated version of the protocol corresponds to the countries needs and reflects diverse capacity to implement it. The protocol is in line with the WHO/UNAIDS Treatment 2.0 policy document (http://www.who.int/hiv/pub/arv/treatment2_lancet_20110303.pdf).

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I. Introduction

HIV is chronic lifelong infection *(1,2)*, with no known cure, and therefore, people living with HIV (PLHIV) have to be followed medically for the rest of their lives. The core component of treatment and care of PLHIV is provision of antiretroviral treatment (ART) *(3,4)*. Optimal ART increases the length and quality of life of PLHIV *(5),* and reduces the onward transmission of the virus *(6,7)*. WHO promotes a public health approach to ART, encompassing the rational selection and sequencing of different drug classes into first and second-line regimens with salvage options; simplified and standardized clinical management; and standardized record keeping in order to preserve therapeutic drug options, minimize adverse drug reactions, maximize patient compliance and thus support the overall goals of providing ART to PLHIV *(8)*.

The major goals of ART are:
- Clinical: prolongation, preservation and enhanced quality of life *(9,10)*;
- Immunological: preservation and improvement (as necessary) of immune function, in order to prevent the onset of opportunistic infections and reduce the risk of AIDS-related cancers;
- Epidemiological: reduction of the risk of onward HIV transmission.

These benefits require achieving the virological goal of a maximum reduction of the viral load for the longest possible time, in order to prevent or delay the development of drug resistance *(11)*.

WHO has produced a series of global guidelines to support ART delivery, which are available on the WHO web site *(12)*. Particular reference is made in this protocol to the guidelines and recommendations for clinical and immunological staging and to the guidelines for ART in adolescents and adults.

Medical history, examination findings, exact ART history, laboratory results, findings from other medical procedures and social circumstances need to be documented for the entire treatment period, which may be years or even decades long. Such records are crucial for the individual patient as well as for retrospective analysis. For such purposes, an electronic record-keeping system is advisable, especially at the clinical level. Confidentiality of medical information should be ensured.

Best treatment and care for PLHIV is based on multidisciplinary clinical teams. The core clinical team provides basic medical case-management and consists of a physician (often an infectious disease specialist), a nurse and a social worker or a non-medical service provider. Each of the team members has a distinct role in providing treatment and care, and their services should be complementary. A network of other specialists and self-help groups should be available to support PLHIV *(13)*.

II. Medical management of PLHIV

Proper medical management of PLHIV is a comprehensive lifelong process focused on the person's needs. It should include:

- initial HIV testing and confirmation of the result;
- clinical evaluation to stage the HIV infection and identification of other conditions requiring care and possible treatment;
- provision of appropriate counselling throughout;
- initiation of ART if appropriate, including adherence support and continued clinical monitoring for effect and adverse drug reaction;
- prevention and treatment of opportunistic infections (OIs), coinfections, including TB, viral hepatitis, sexually transmitted infections (STIs) and comorbidities;
- access to psychological and social support if required;
- opioid substitution therapy (OST) if required and permitted by local law;
- sterile needles in exchange programs if required; and
- referral to provide continuity of treatment and care if initial care centre is unable to do so.

1. Initial patient evaluation

The initial evaluation of a PLHIV aims to determine the full status of the HIV disease, to develop a basis for further clinical management and referral to non-medical services as appropriate.

Initial patient evaluation should include:

- confirmation of HIV infection status and establishment of time of infection, if possible
- a detailed personal, family and medical history
- a physical examination
- laboratory and other examinations
- specialist examinations, as appropriate
- clinical and immunological staging.

1.1. Personal, family and medical history

People newly diagnosed with HIV infection or PLHIV who have been transferred after having had their long-term care and ART initiated elsewhere should provide a complete history before physical examination (Table 1) (strong recommendation, C).

TABLE 1.	MEDICAL HISTORY INFORMATION REQUIRED AT INITIAL PATIENT EVALUATION
General information: • date of assessment • patient's name • date of birth • country of origin • gender	
Testing information: • date of first positive HIV test • reason why the test was done • last HIV-negative test, if known	
HIV exposure risk and transmission category (if known): • injecting drug use • sexual (heterosexual, homosexual, explore types of sexual contact [oral, vaginal, anal] as appropriate) • blood or blood product transfusion, organ and tissue transplantation • mother-to-child transmission • occupational exposure (describe) • unknown • HIV and ART status of sexual partner(s) (if known) • risk factor of sexual partner(s) (if known)	

Calendar time and place (country) of acquisition of HIV infection (most probable or known[a])
History of HIV treatment and care – if relevant: (see Annex 1) • time and place of previous care and treatment for HIV and related conditions • ART drug regimens used, with dates of all changes in regimen (if any) and reasons for change • adverse drug reactions experienced (if any) • adherence and possible interruption of ART • laboratory data: CD4 cell count, VL, liver function enzymes, renal function assessment (S-creatinine and hence estimation of glomerular filtration rate [eGFR] + proteinuria), haemoglobin, leukocyte, lymphocyte and neutrophil count, in chronological order since care was initiated) • results of any previous resistance tests
HIV-related illnesses and conditions: • TB (history of, or current active infection) • other pulmonary infections • invasive viral, bacterial, protozoal or fungal infections • prior or chronic ongoing viral hepatitis B and C (HBV, HCV) infection • cancers (history of or currently active disease) • anal, penile or vaginal condylomas, • other
Other illnesses and conditions: • hospitalization • surgery • kidney or liver diseases • mental health (depression, dementia, manic depression, etc.) • endocrinological disorders • STI, including herpes simplex, syphilis, gonorrhoea, *Chlamydia*) • vaccinations (influenza, *S. pneumoniae*) • allergies including drug allergies (sulfonamides, penicillin) • body changes
Family medical history (diabetes, hypertension, cardiovascular disease [CVD], malignancies, tuberculosis, etc.)
CVD and risk factors thereof (smoking, hypertension, diabetes, etc.)
Exposure to TB (personal and household TB contacts; result of previous tuberculin skin test or preferably IFN-gamma release assay **[**IGRA**]** results)[b] **Travel to endemic areas** for protozoal (leishmaniasis, Chagas' disease) or fungal infections (histoplasmosis, coccidiomycosis)
Current medications including ART, opioid substitute therapy (OST), comorbidities (prevention or treatment), etc.
Substance use: • illicit drug use – past and ongoing, type of drugs used (heroin, cocaine, methamphetamine), method of use (injecting, smoking, etc.) • alcohol consumption (prior overuse and units consumed in last week)
Reproductive and sexual health: • current contraceptive methods (for female PLHIV) • pregnancies (past, current, planned) • sexual practices (oral, anal, vaginal) • erectile dysfunction
Social history • living situation (partners/spouses/family members, children, etc.) • employment and occupation • housing • support networks (social and medical insurance, community groups, people knowing patient's HIV status, etc.)

[a] Useful for epidemiology, subtype of virus and possibly a drug resistance profile.

[b] For further evaluation of TB please refer to Protocol 4, *Management of tuberculosis and HIV coinfection (in press)*.

1.2. Physical examination

The physical examination should document presenting symptoms, signs and reproducible results so that other physicians can determine changes in status (strong recommendation, C). A standardized history and examination questionnaire is preferable; see Table 2.

Table 2.	**Initial physical examination**
General appearance: • height, current and usual weight • body morphology (e.g. lipodystrophy) • overall fitness using standardized scale (e.g. Karnofsky index)	
Vital signs: • blood pressure • temperature • pulse • respiratory rate	
Lymph nodes (location of enlargement – if any)	
Skin (entire body) in particular, assess for: • active or former herpes zoster • liver disease • Kaposi's sarcoma (number of lesions, substance of lesions, lymphatic involvement) • seborrhoeic dermatitis • injection sites in injecting drug users (IDUs)	
Eyes: • visual impairment • paresis of eye muscles	

Oro-pharynx:
• lesion in oral cavity and dental status
• signs of:
  • oral candidiasis
  • oral hairy leukoplakia
  • primary syphilis	

Thorax and lungs: • signs and symptoms (respiratory rate, expansion, percussion, auscultation, cough, dyspnoea) • form of thorax • buffalo hump	
Breast examination (in female **and male** PLHIV) to identify tumours	
Cardiac examination – evidence of ischaemic heart disease (IHD), congestive heart failure or endocarditis (especially in IDUs)	
Abdominal examination • shape • consistency, size and shape of liver and spleen (enlargement?) • other palpable enlargements • bowel movement • tenderness • rigidity • ascites	
Genital and anal region examination for signs of: • herpes simplex virus infection • syphilis • Human papilloma virus (HPV), (*Condylomata acuminatae*, cervical or anal cancer), • other STIs	
Legs (joint mobility, venous insufficiency, arterial insufficiency, lipoatrophy)	
Neurological status (cognitive function, pareses, also signs of neuropathy)	
Mental status (conscious, answer relevant to questions, disillusional, tardive response)	

1.3. Laboratory and other examinations

A standard battery of laboratory examinations is recommended (Table 3), additional tests maybe warranted if available (Table 4) and involvement of other specialists required (Table 5) (recommendation strong, C).

Table 3. Laboratory testing

HIV-related testing

- HIV serological testing (enzyme-linked immunosorbent assay [ELISA] or rapid blood test), followed by confirmatory test (western blot or other reliable test); a second, separate sample for confirmatory testing
- CD4 cell test (absolute count and percentage) – evaluates severity of immunodeficiency *(14)*
- Level of HIV-RNA (copies/mL) in plasma (the viral load [VL]) – reflects level of replication of HIV in the body [a] *(15,16)*

Other infectious disease testing

Routine testing:

- test for syphilis: venereal disease research laboratory (VDRL); or *Treponema pallidum* Ig EIA
- serological tests for hepatitis A, B and C viruses (HAV, HBV and HCV)[b] – i.e. HAV antibodies, hepatitis B virus surface antigen (HBsAg; if positive do HBV-DNA by PCR if available – otherwise HBeAg – and consider delta-antibody screening; if HBsAg negative, do HBs antibodies and if also negative, vaccinate) and HCV antibodies (if positive do HCV-RNA by PCR if available)
- toxoplasma immunoglobulin G (IgG) serological test – if negative, provide counselling to avoid infection; if positive and signs of CNS infection, consider toxoplasma encephalitis
- CMV immunoglobulin G (IgG) serological test – if negative, provide counselling to avoid infection; if positive and low CD4 cell counts, consider CMV retinitis or gastroenteritis
- pap smear for women once annually and consider annual screen for anal cancer in persons having engaged in anal sex.
- if signs of STI: vaginal, urine and anal sampling for gonorrhoea and C*hlamydia trachomatis*
- if signs of meningitis/encephalitis and CD4 cell count is < *200/* mm^3: *Cryptococcus* antigen in serum and CSF

General laboratory testing:

- complete blood count (leucocyte, lymphocyte and neutrophil and platelet count; erythrocytes, Hb)
- liver function – alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatise (elevated levels signify ongoing liver disease, but chronic HCV infection may cause severe liver disease without affecting these enzymes)
- bilirubin – sometimes elevated if ongoing liver disease; some ARVs (IDV, ATV) also elevate bilirubin (without affecting liver function enzymes) and this does not signify liver damage
- renal function – S-creatinine; calculate eGFR (http://www.cphiv.dk/TOOLS/tabid/282/Default.aspx); proteinuria
- lactate dehydrogenase (LDH) – general damage/turnover of cells (elevated if lymphomas, several pulmonary infections, myocardial infarction, muscle damage, etc.)
- glucose – if above upper limit of normal do glucose test on a fasting sample
- amylase – to detect pancreatitis; maybe normal in chronic pancreatitis
- pregnancy test, if relevant

[a] A single quality-assured laboratory is preferable.

[b] For further information on testing of hepatitis, please refer to Protocols 6 and 7, *Management of hepatitis C and HIV coinfection (2007)* and *Management of hepatitis B and HIV coinfection (2011 revision)*.

Table 4.	Other examinations

- cholesterol – total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) + triglycerides (TG); if above upper limit of normal, do fasting; elevated levels maybe congenital, related to diet, obesity (low HDL-c and high TG), or be drug-induced – calculate 10 year CVD risk using equation (http://www.cphiv.dk/TOOLS/tabid/282/Default.aspx)
- test of HIV for presence of drug-related mutations (genotypic resistance test) *(17–22)*
- HLA B*5701 typing in subjects for whom treatment with abacavir is considered *(23)*
- chest X-ray
- blood for *M. tuberculosis*-specific IFN-gamma release assay (IGRA) (preferred) or tuberculin skin test (alternative) for those with no TB symptoms and no history of TBc (positive result signifies previous TB latent TB infection or prior TB vaccination; chance of false negative results if CD4 cell count is low) [a] *(24)*
- sputum-smear microscopy if signs and symptoms of active TB are present [a]
- funduscopic examination, especially if low CD4 cell counts *(25)*
- ECG – arrthymias prolongation of QT (methadone?) and PR interval, QT-depression (IHD), signs of prior myocardial infarction, use for reference during continued care in case of emerging cardiac symptoms *(26)*

[a] For further information please refer to Protocol 4, *Management of tuberculosis and HIV coinfection (in press)*.

Other examinations may be necessary (see Table 5), depending on individual known or suspected comorbidities, for example, coinfection with HBV or HCV (ultrasound, liver biopsy), gastrointestinal (GI) tract disease (endoscopy of the upper and lower GI tract, document abnormalities by photo), diarrhoea (microbiological stool examination), CNS disease (lumbar puncture, computer tomography or magnetic resonance imaging of brain tissue), pulmonary disease (tracheal aspirate, bronchoscopy), or skin disease (skin biopsy). If these are suspected, it is advisable to consult with experts. HAV and/or HBV vaccinations should be considered if indicated based on serological results.

Table 5.	Specialist consultations if required

Appropriate specialists should be consulted as warrented:

- hepatologist if signs of liver dysfunction in PLHIV coinfected with HCV or HBV
- neurologist if signs of CNS disease or peripheral polyneuropathy
- psychiatrist if signs of mental disorders
- ophthalmologist if evidence of impaired vision (retinal examination)
- endoscopist and bronchoscopist (if signs of GI and pulmonary disease, respectively)
- gynaecologist (pelvic examination including a Pap smear recommended every year for all female PLHIV)
- endocrinologist (in case of evidence of diabetes, thyroid disease, etc.)
- cardiologist (if signs of IHD)
- nephrologist (if eGFR<60 ml/min – in particular if proteinuria)
- proctologist to detect anal condylomas or carcinomas
- oncologists and haematologist in case of suspicion or diagnosis of relevant malignant disease
- other specialist consultations as needed.

2. Counselling on issues related to living with HIV

Patient counselling is an essential component of patient management strategy and patient-health care provider relationships (strong recommendation, C).

Counselling should start with the assessment and discussion of the patient's social and psychological conditions, which may be predictors of cooperation during treatment. These include:

- partnership status and quality
- employment status, type of work and conditions
- people who are informed and should be informed of the HIV status
- people with whom health care workers can discuss the patient's health-related matters
- familial relationships
- lifestyle factors and drug dependencies that might interfere with treatment *(27–29)*.

Health care providers responsible for the care of PLHIV should ensure that certain information is discussed with and understood by every patient under continued care. The counselling may be provided by physicians, nurses or other professionals; if more than one person on the team is involved, it is critical to ensure that the counselling be done in a coordinated and consistent way, with explanations that the PLHIV can intuitively understand.

The following are the key issues:

- Reduction of the risk of HIV transmission must be carefully explained, and measures such as safe sex, safe injecting practices must be reinforced *(30–33)*.
- The importance of disclosure of HIV status to sexual partners, and possibly friends and family in order to obtain psychological and treatment support, prevent HIV transmission and allow for testing should be stressed. Disclosure of HIV status to anyone other than care-givers is *solely* up to the decision of the PLHIV (unless required by law). The health care provider team should counsel the PLHIV to ensure that any possible negative consequences (stigmatization, discrimination, exclusion from social networks, limitations on ability to travel and obtain social and insurance benefits) of the disclosure are minimized to the extent possible. In some circumstances it may be advisable to limit the disclosure.
- The availability of treatment, its benefits and preparation should be discussed, as well as its long-term consequences and the importance of adherence.
- Knowledge about the signs and symptoms of possible opportunistic infections (OIs) should be conveyed, and a contact given to be consulted if an OI should appear. For further information, see Protocol 2, *Management of opportunistic infections and general symptoms of HIV/AIDS (2007)*.
- The benefits of stopping illicit drug use should be emphasized, if applicable. If a PLHIV is unable or unwilling to stop, the merits of harm-reduction measures should be discussed, including reducing the quantity of drugs consumed, avoiding injecting drugs, not sharing needles, syringes or other injecting paraphernalia and initiating drug dependence therapy (such as OST). The irregular lifestyle sometimes associated with continued use of illicit drugs has been shown to impair the ability of the PLHIV to adhere to ART *(34 35)*, and it is therefore a shared responsibility of the PLHIV and the health care team to ensure that any negative impact of continued illicit drug use on the HIV treatment be minimized. For more information, please refer to Protocol 5, *HIV/AIDS treatment and care for injecting drug users (2007)*.
- Reduction of the risk of infection with other pathogens including STIs and viral hepatitis should be discussed. (See section II.3 below.)
- Based on the assessment of social conditions, healthy daily habits – sleep, nutrition, and exercise – should be encouraged.
- PLHIV about to initiate ART should be counselled on:
  - adherence (See section II.4.3 below.)
  - adverse ARV drug reactions (See section II.5.5 below.)
  - drug interactions (See section II.5.6 below.)
  - use of reliable contraception if the ARV regimen contains efavirenz (EFV) (For further information refer to Protocol 9, Support for sexual and reproductive health in people living with HIV/AIDS (2007)).
  - the processes by which care and treatment will be provided at the site, including the patient's responsibilities (compliance with visit scheduling, commitment to having a supply of the prescribed drugs available at all times, maintaining health care insurance, etc.)
- PLHIV should also be informed about any legal responsibilities, their rights and be referred to other appropriate services.
- PLHIV should be informed of vaccination risks (including travel-related) and occupational risks. (For details, please see Protocol 12, *Immunization of people living with HIV/AIDS and people at risk for HIV (2007))*.

3. Prevention of opportunistic and other infections

- Prevention of active tuberculosis is a priority for PLHIV living in or originating from areas with significant ongoing TB transmission. For more information please see Protocol 4, *Management of tuberculosis and HIV coinfection (in press)*.
- As chronic HBV/HIV and HCV/HIV coinfections are common and present further medical challenges, their prevention should be emphasized.
- PLHIV should be immunized against HAV, HBV, influenza and *S. pneumoniae* if not previously infected and/or immunized. For further information, please refer to Protocol 12, *Immunization of people living with HIV/AIDS and people at risk for HIV (2007)*.
- All patients with a CD4 cell count less than 200 cells/mm^3 should be given chemoprophylaxis against certain opportunistic infections, in particular *Pneumocystis jirovecii* pneumonia (PCP) and toxoplasmosis. Chemoprophylaxis should be maintained until the CD4 cell count has been above 200 cells/mm^3 for more than 3 months after initiating ART. For more information please refer to Protocol 2, *Management of opportunistic infections and general symptoms of HIV/AIDS (2007)*.

4. Antiretroviral treatment

4.1. Initiation of ART

The best time for starting ART is under discussion *(36–40)*. A review of randomized controlled trials, cohort studies and guidelines shows a widespread view that clinical staging (WHO clinical stage 3 or 4) and CD4 cell counts are the best primary markers for this *(37,39–50)*. Prior to starting ART, support to ensure adherence should be initiated; see section II.4.3 below.

4.1.1. Clinical and immunological considerations

Table 6. Recommendations for initiating ART in PLHIV

Target population	WHO clinical stage[a]	CD4 cell count	Recommendation[b]
Asymptomatic[c] persons	**1**	≤350/mm^3, [g]	Treat (strong, A)
	1	≥350/mm^3, [g]	Defer treatment [g] (moderate, B)
Symptomatic[c] persons	**2**	≤350/mm^3, [g]	Treat (strong, A)
	2	≥ 350/mm^3, [g]	Defer treatment [g] (moderate, B)
	3	Regardless of CD4 cell count	Treat (strong, A)
	4	Regardless of CD4 cell count	Treat (strong, A)
Chronic HBV requiring treatment [d]		Regardless of CD4 cell count	Treat (moderate, B)
Active Tuberculosis [e]		Regardless of CD4 cell count	Treat (strong, C)
HCV infection requiring treatment		< 500/mm^3	Treat (moderate, B)
		≥ 500/ mm^3	Consider Treat (optional, C)
Pregnant women [f]		Regardless of CD4 cell count	Treat (strong, A) – initiation can be postponed to second trimester if woman is healthy and have CD4 cell count > 350/mm^3

[a] See Annex 2 for description of the clinical stages.

[b] The lower the CD4 cell count below 350/mm^3, the higher the risk of severe HIV-associated disease and death if left untreated – if resources for ART are limited, priority should be given to those in the population with lowest CD4 cell count.

[c] The concept of "symptoms" alludes solely to diseases associated with WHO clinical staging and not symptoms from other comorbidities.

[d] See Protocol 7, *Management of hepatitis B and HIV coinfection (2011 revision).*

[e] See Protocol 4, *Management of tuberculosis and HIV coinfection (in press).*

[f] Pregnancy in an HIV-positive woman is an absolute indication for ART to reduce risk of MTCT irrespective of the CD4 cell count; initiation of ART can be postponed to early in the second trimester if in WHO stage 1 or 2, and CD4 cell count is above 350 cells/mm^3 – it is controversial whether to discontinue ART after the pregnancy in asymptomatic women that initiated ART during pregnancy with a CD4 cell count above 350 cells/mm^3 – see the Recommendations for a public health approach *Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants (51).*

[g] When the CD4 cell count decreases to 400–450 cells/mm^3, begin discussions with the patient on the advancing need to initiate ART and on preparations for it. Ensure regular follow-up visits and checks of CD4 cell count.

The decision to initiate ART should preferably be based on two independently measured CD4 cell counts, ideally at least seven days apart because of variability in the CD4 cell count itself and to rule out laboratory mistakes and other sources of variability (for example, concurrent illnesses). In case of a concurrent acute illness, the CD4 cell count should be repeated only after the illness is resolved. Therapy should not, however, be delayed if a PLHIV is unwell or if the second count cannot readily be performed. If the CD4 cell count is not available, the decision to initiate ART can still be made on clinical grounds alone for WHO clinical stage 3 or 4 illness.

The CD4 cell count determined at the onset of ART (ideally when the patient is free from any active major OI) is a critical value in determining prognosis and monitoring the subsequent immunological response and assessing the potential use of nevirapine in first-line therapy (see II.4.2).

4.1.2. HIV-RNA load (VL) considerations

In HIV-positive people who have not started treatment, higher VL is associated with more rapid loss of CD4 cells *(14,52,53)*. In asymptomatic PLHIV with CD4 cell counts approaching the 350-cells/mm^3 threshold for initiation of ART, it is especially important to ensure regular visit follow-up and assessment of CD4 cell count levels (maximum three months intervals) in persons with high VL (particularly >100 000 copies/ml).

High VL alone is not an indication for initiating ART. It is helpful for the future monitoring of ART response to have a VL value taken just prior to commencing ART (see section II.4.4 below).

VL testing is more expensive and may be less accessible than CD4 cell counts. The absence of VL data should not be a criterion for delaying the start of treatment, or used as a reason for treatment exclusion. If resources to perform VL are limited, priority should be given to using the available resources to assess ART response (see section II.4.4) as opposed to performing serial assessments of VL in people that have not yet initiated ART.

4.1.3. Drug resistance testing considerations

Prevalence of drug resistant HIV in PLHIV that have not yet initiated ART (i.e. transmitted drug resistance) varies in different countries and is linked to several factors, including the type and duration of ART availability and how effective ART was at maintaining complete suppression of VL in the population from which the PLHIV contracted the HIV infection *(17–19,54)*. In western Europe, where ART has been available for more than two decades, many PLHIV harbour acquired drug resistant HIV, but since an ever larger proportion of the population on ART have undetectable low VL values due to recent advances in treatment the relevance for ongoing transmission is unclear *(55)*. The prevalence of transmitted drug resistant HIV has decreased in the last 10 years from above 10% to levels well below 10% in most areas. However, in settings such as this it remains recommended to perform a drug resistance test as soon as possible after HIV diagnosis. In eastern Europe, the risk of HIV drug-resistant virus transmission is less well studied *(56)* but likely remains low, and the first-line ART regimen recommended below (section II.4.2) can be assumed to be effective for treatment of naïve PLHIV.

It is important to have population-based HIV drug resistance strategies in place to monitor for the appearance and spread of HIV drug resistance and to act on the early warning indicators for drug resistance emergence in order to minimize its appearance and spread *(57,58)*. WHO does not recommend individual drug resistance testing prior to initiation of ART in settings where only one uniform national first-line regimen is provided in the public sector because no results will influence the initial choice of ART. In such countries, if there is flexibility in the choice of drugs to be included in the uniform national first-line regimen, sentinel surveys demonstrating resistance above the threshold of 5% at population level should be considered. Refer to Annex 4 for additional information on resistance testing as well as a listing of specific mutations, focused on in the Global HIV drug resistance surveillance *(59)*. Where resources permit, and the public sector provides more than one first-line regimen, drug resistance testing of individual patients at the start of care may help determine the choice of subsequent optimum ART, but cost and availability will likely limit the widespread use of resistance testing in many settings.

4.1.4. Age considerations

In addition to the list of diseases in Annex 2, HIV itself – or the associated immunodeficiency – may increase the risk of contracting several age-associated diseases or adversely affect their management *(60–70)*. Liver disease, particularly in PLHIV coinfected with HBV or HCV *(60,61)* (see protocol 7 *Management of Hepatitis B and HIV Coinfection (2011 revision)* and protocol 6 *Management*

of Hepatitis C and HIV Coinfection (2007), is a good example, and this is why ART is generally recommended for such patients even if the CD4 cell count is in the 350–500 range (see Table 6).

There is a debate on whether HIV causes (and, by implication, that ART may prevent) other types of age-related diseases, including CVDs *(64,69,71–73)*, chronic obstructive pulmonary disease *(74,75)*, tubular or glomerular renal disease (in addition to the well-established HIV-associated nephropathy) *(68,76–80)*, neurocognitive disorders (other than HIV encephalopathy) *(81–85)*, and non-AIDS-defining cancers *(66,67,86,87)*. However, there is insufficient evidence to include stratifications for the risk of contracting these diseases when recommending when to start ART for asymptomatic PLHIV. It is unknown whether the benefit:risk ratio favours using ART in these circumstances. Conversely, in PLHIV that have developed renal disease, severe neurocognitive impairment or a nonAIDS-defining cancer requiring extensive chemotherapy and/or radiotherapy, consideration could be given to initiating ART irrespective of the CD4 cell count (moderate recommendation, B).

4.1.5. HIV transmission considerations

ART reduces the risk of HIV transmission *(88,89)*, and this indication for use of ART is well-established when used to reduce the risk of MTCT *(6)*. Cohort studies suggest that ART reduces the risk of sexual transmission *(7,90–93)*, and it is plausible that transmission risk by needle sharing is likewise reduced *(30)*. Estimates suggest that use of ART (and plasma VL < 50 copies/ml) reduces the risk of sexual HIV transmission to a low level *(94–95)*.

If resources allow, and the patient insists, consideration should be given to initiating ART irrespective of CD4 cell count to those may engage in repeated unprotected sex acts with a HIV-uninfected person, provided that the PLHIV has understood that ART – once initiated – should be maintained for life and may cause significant adverse drug reactions (moderate recommendation, A). In all other settings, it is unclear whether ART is an effective public health intervention for reducing the risk of HIV transmission. Initiation of ART should not replace the use of the usual preventive measures, particularly condoms.

4.1.6. Considerations for initiation of ART in PLHIV with an OI

ART should be initiated for people with OIs irrespective of the CD4 cell count (Table 6). Deciding the exact time for initiating ART depends on the type of OI (availability of medical treatment, degree of severity), the potential for drug-drug interactions *(96),*[1] any adverse drug reaction profile among the drugs used to treat the OI and the ART, the patient's degree of immunodeficiency, due to the risk of contracting other OIs or developing immune reconstitution inflammatory syndrome (IRIS, see section 5.3) *(97–99)*. Several randomized controlled trials have recently informed this discussion *(100–102)*.

It is recommended to initiate ART as soon as possible after treatment of the OI has been initiated and early signs of reasonable tolerability thereof have been demonstrated (usually no later than 2 weeks) (strong recommendation, A). The urgency of this recommendation is strongest for PLHIV with a CD4 cell count < 100/mm^3.

4.2. First-line ART regimen

It is recommended that two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and efavirenz (EFV) (a non-nucleoside reverse transcriptase inhibitor [NNRTI]) be combined in the first-line ART regimen. If EFV cannot be used, a ritonavir-boosted protease inhibitor (PI/r) or nevirapine (NVP) are alternatives, and use of a third nucleoside or raltegravir (RAL) is acceptable (see Table 7). There are several ways of combining the NRTI backbone. For recommended dosages, please refer to Annex 5.

[1] (http://www.hiv-druginteractions.org)

Table 7.	Recommended first-line ART – preferred, alternative and acceptable drugs			
	ART regimen	**NRTI combination**		**3rd drug**
		First drug	**Second drug**	
Preferred	2 NRTIs + EFV	FTC[d] or 3TC[d]	TDF[d]	EFV
Alternative	2 NRTIs + 1 PI/r[a] or NVP		ABC or ZDV[c]	PI/r[a] or NVP[b]
Acceptable			ZDV or TDF[c]	ABC or TDF or RAL

[a] ATV/r or LPV/r (preferred), DRV/r (alternative) and FPV/r & SQV/r (acceptable).

[b] NVP is an alternative drug to use in resource-limited settings, because of its low cost, availability as FDC and the long-term experience with the drug's efficacy and safety profile. However, NVP may cause severe adverse drug reactions early on after its initiation and safer alternatives exist in Europe. Also, NVP is safest to use in people with low CD4 cell count.

[c] Only two 3-NRTI combinations should be used, namely 3TC or FTC+ZDV+ABC and ZDV + 3TC or FTC + TDF; these combinations should only be used if more effective and safer regimens are not available or contraindicated.

[d] Preferred combination in PLHIV with chronic HBV infection (irrespective of whether HBV requires treatment or not).

[e] d4T and ddI are not listed in the table, but can be used in specific situations: d4T is an acceptable choice if there are no other safer alternatives since the drug has a good short-term tolerability, is available as FDC and is the least costly of all available ARV drugs – if used only for a short duration (max 6 months); ddI is an alternative choice to d4T but also associated with high risk of mitochondrial toxicity.

For recommended dosages of ARVs, please refer to Annex 5.

4.2.1. NRTI combination considerations

The backbone of first-line ART is a combination of two NRTIs:

- One of the NRTIs should be lamivudine (3TC) or emtricitabine (FTC), which have similar efficacy and no clinically significant adverse drug reaction profile *(103–105),* and they can be used interchangeably. Drug resistance develops quickly if ART is not fully suppressive.
- The second NRTI should be one of the five drugs mentioned below, which are all effective antivirals (fairly comparable intrinsic efficacy if tolerated), and share a slow rate of resistance accumulation (although the signature mutations differ) when used in an ART regimen that is unable to fully suppress HIV replication. Their adverse drug reaction profiles differ, however.
  - A non-thymidine analogue
    - Tenofovir (TDF) is better tolerated than ZDV *(106–107)* and d4T (see below). The primary adverse drug reaction is acute renal disease (proximal tubular dysfunction characterized as a Fanconi's syndrome), which is relatively rare (0.5–1%) and may emerge early after initiation *(108–110)*. Possible progressive renal toxicity remains unclear *(111)*. TDF may also adversely affect bone mineralization *(112)*.
    - Abacavir (ABC) has less intrinsic efficacy than TDF in patients with high viral loads *(113,114)*. ABC is better tolerated than ZDV *(115)* and d4T (see below). In persons with a specific tissue allele (HLA B*5701) however, the drug causes a hypersensitivity reaction (HSR) usually within the first six weeks after initiation *(23,116)*. Genetic testing to identify people with this haplotype is hence recommended before using ABC, and the drug should not be used in people with the allele. Caution should be applied when using it in combination with other drugs that cause similar side effects (e.g. co-trimoxazole, nevirapine, fosamprenavir). The prevalence of this allele is 3–10% in people of European descent, and substantially lower in those of African or Asian descent. Ongoing use of ABC may be associated with excess risk of ischaemic heart disease in people at high underlying CVD risk *(117)*, although this issue remains controversial.
    - Didanosine (ddI) has been shown to have a favourable virological response in combination with 3TC (or FTC) and EFV *(118, 119)*. DdI may cause peripheral neuropathy and pancreatitis *(120,121)*, and observational studies have found an association between its long-term use

and the risk of non-cirrhotic portal hypertension *(122)*. The drug is fairly inexpensive, and may be considered as an alternative to d4T (see below) if other safer and better studied drugs are not available.

- A thymidine analogue
  - Zidovudine (ZDV, also known as AZT) has been in use for more than two decades *(123–126)*. It may cause nausea, anaemia and neutropenia within the first weeks after initiation. After several years of use it can lead to lipodystrophy *(107–127)*.
  - Stavudine (d4T) is cheaper than ZDV, has a good GI tolerability, does not have bone marrow toxicity and is consequently widely used in many countries. However, d4T has a poor long–term adverse drug reaction profile consisting of peripheral neuropathy, lactic acidosis and lipoatrophy *(128–135)*. Because of this, d4T is not recommended for general use. However, these reactions only appear after several months of use, and short-term use of d4T (up to 6 months) may be acceptable in settings where there is a temporary lack of access to safer alternatives. The dose of d4T is 30 mg BID irrespective of body weight *(136)*.

The non-thymidine analogues are preferred over the thymidine analogues (moderate recommendation, A), in the following order of preference: TDF, > ABC, > ZDV and > ddI and d4T.

The advantage of TDF and ABC is their better tolerability and better resistance profile. Use of the latter as a first-line drug potentially allows a greater choice of NRTI combinations to support second-line protease inhibitors (PIs) should the first line regimen fail. Both drugs only need to be given once daily (QD), as opposed to twice daily (BID) for the thymidine analogues. The disadvantages are cost, availability and licensing.

Other NRTIs and combinations are not recommended for first-line ART (e.g. the combination of TDF and ddI *(137–140)*. The following combinations are strictly contraindicated:

- ZDV and d4T
- 3TC and FTC
- ddI and d4T, especially in pregnant women.

4.2.2. Third-drug considerations

Drugs from one of three classes maybe combined with the two NRTIs to form a first-line ART regimen, namely a NNRTI, a protease inhibitor, raltegravir (an integrase inhibitor) or the combination of three NRTIs.

- Three NNRTIs are currently available for use in ART; only one should be used at a time. Their adverse drug reaction profiles differ, as does their preference and place in the sequence of ART.
  - Efavirenz (EFV) has high intrinsic efficacy *(124,141–145)*, and its interaction profile allows it to be used with TB medications without dose adjustment. The two primary concerns with the drug are debilitating adverse effects in the central nervous system (CNS) and the potential for teratogenicity *(146)*.[2] CNS adverse drug reactions are frequent, and appear promptly once the drug is started but gradually reduce in intensity. PLHIV should be carefully informed of potential for CNS side-effects, and should be advised to only take the drug just prior to sleeping. EFV should not be used by those with a history of severe psychiatric disorder, as the drug may lead to the recurrence of the condition. Animal experiments suggest the potential for teratogenicity, and EFV should only be used in non-pregnant women of child-bearing potential if they use effective contraception. Notably, EFV is not contra-indicated in pregnancy after the first trimester (see Protocol 10 *Prevention of HIV transmission from HIV-infected mothers to their infants (in press)*. EFV significantly alters methadone levels and its use along with methadone may precipitate symptoms of withdrawal requiring increases in methadone dose. Conversely, discontinuation of EFV in person on methadone may result in methadone toxicity, which may be life threatening.

[2] See also www.APRegistry.com.

- Nevirapine (NVP). The intrinsic efficacy of NVP is probably comparable to that of EFV and ATV/r (147–150). However, NVP may lead to severe skin rash and toxic hepatitis, which can emerge within the first six weeks after start of treatment *(151–155)*. The risk of this side effect is elevated in women (relative to men) and in persons starting the drug at higher CD4 cell counts. Because of this, NVP should be used with caution and only if no safer drugs are available for those with moderate to severe liver impairment, HBV or HCV coinfection, women with CD4 cell count > 250/mm^3 and men with CD4 cell counts > 400/mm^3 as part of the initial regimen. Conversely, this CD4 cell count is not relevant in PLHIV already suppressed on ART for whom a switch to NVP is being considered *(155)*. The drug is dosed in half the recommended dose over the first two weeks for better tolerance. ALT levels should be measured after initiation (particularly in people with already impaired liver function, see Table 10) and NVP should be discontinued if ALT increases to > five times of upper level of normal. NVP should not be used with rifampicin for co-treatment of TB, and the drug affects the dosing requirements of methadone.
- Etravirine (ETR) should only be used as part of ART beyond the first-line (moderate recommendation, C) (see under salvage therapy, and section II.4.6 *(156–157))*.

EFV is preferred over NVP (moderate recommendation, B). ETR should only be used as part of lines of ART beyond the first line (moderate recommendation, C); see section II.4.5. NNRTIs are contraindicated for treating HIV-2, as it is naturally resistant to this drug class (strong recommendation, B) *(158)*.

Both EFV and NVP can be administered once daily *(147,159)*. If the regimen is not fully suppressive, drug resistance develops quickly. The drug resistance profile is shared and hence there is complete cross-resistance *(160)*. Both drugs have important adverse reactions that require careful attention, in particular in the early phase of use. Besides a more serious adverse effect profile, NVP has a potential for drug-drug interactions. However, the prospect for either drug is good after three to four months of effective and safe use.

- PI/r. It is recommended to use an active PI in combination with low dose ritonavir (PI/r) to increase the plasma concentration (161–163), but not all PIs are safely amendable to this principle. Within a public health approach and within the public sector in many countries PI/r should be reserved for second-line ART. PIs are more expensive than NNRTIs. The alternative to EFV is NVP. However, in many places in Europe, PI/r is used as an alternative to EFV as part of first-line ART. If PI/r are considered as part of first-line ART, there are several options: atazanavir (ATV/r) (164,165), lopinavir/r (LPV/r) (166–168), darunavir (DRV/r) (169–170), fos-amprenavir (FPV/r) (171) and saquinavir (SQV/r) (161,172). ATV/r and LPV/r can be dosed QD (173,174). ATV/r may cause jaundice and nephrolithiasis (171–175), LPV/r nausea and diarrhoea, DRV/r rash, FPV/r rash and diarrhoea. PIs may also elevate the risk of CVD (176). Generally, PI/r cannot be used with rifampicin for co-treatment of TB – if rifabutin is used instead (dosed as 150 mg x 3 per week), it is possible. There is risk of interactions with drugs used to treat other comorbidities (see Annex 6). Resistance to PI/r is slow to develop, and hence PI/r is preferred if low adherence is anticipated or NNRTIs are contraindicated.

- Integrase inhibitor. One drug from this class, raltegravir (RAL) has comparable efficacy to the preferred first line regimens (143,177). No severe adverse reactions have yet been ascribed to this drug. RAL is dosed BID. Due to cost consideration, limited information on long-term safety and low genetic barrier to resistance, this drug should generally be reserved for salvage therapy in settings using a public health approach to ART.

- There are two triple NRTIs regimens to consider, but since both are less effective than the combination of drugs from different drug classes, they are only recommended if other more effective regimens are not available.
  - ZDV+3TC+ABC has inferior viral efficacy than the preferred first-line ART regimens, in particular for PLHIV with high VL *(126,178,179)*.

- ZDV+3TC+TDF is relatively effective compared to the preferred or alternative first–line ART regimens. However, the combination has been studied in RCTs conducted in resource-constrained areas *(180)*, and further evidence will be forthcoming.

The following drugs are not recommended to be used as alternatives to the preferred first-line drugs.

- Other triple NRTI combination regimens have inferior virological efficacy – e.g. the combination of TDF+ABC+3TC (181) or d4T+ddI+ABC (182,183) – or have not been sufficiently extensively tested.

- Indinavir causes retinoid toxicity-like symptoms, kidney stones and renal impairment (124,161).

- Nelfinavir (NFV) has variable absorption from GI tract leading to viral failure (166).

- Maraviroc (MRV) (184,185) requires assessment of viral tropism (now possible to do a genotypic assessment in some virological laboratories) as it is only effective against CCR5-tropic HIV, and is costly.

- Enfuvirtide (ENF) has not been studied in early ART, requires subcutaneous administration, is costly, and is now rarely used.

4.2.3. Choice of first-line ART regimens in special situations

- *Chronic HBV infection:*
  The combination of TDF and FTC (or 3TC) (186,187) is preferred (strong recommendation, A). Both drugs are also effective against HBV. If 3TC or FTC are used in combination with either of the thymidine analogues (AZT, d4T) or ABC, HBV acquires drug resistance quickly *(188)*. The risk of liver toxicity from antiviral drugs is exacerbated in patients with chronic HBV infection *(189,190)*. See also Protocol 7, *Management of hepatitis B and HIV coinfection (2011 revision)*.

- *Tuberculosis:*
  Rifampicin reduces exposure to NVP (191), EFV (192,193), all PI/r (194–197) and RAL, and it is recommended to replace rifampicin with rifabutine for PLHIV receiving ART (strong recommendation, B). If rifabutin is not available, the preferred choice is EFV+2NRTIs *(193,198,199)* or a 3NRTI regimen (ZDV+3TC+ABC, ZDV + 3TC + TDF or ZDV + FTC + TDF). If the alternative is used, it is furthermore recommended to switch to another more effective ART regimen once rifampicin is no longer used as part of the TB treatment regime.

- *Women of child-bearing potential:*
  EFV should only be used if these women use effective contraception, otherwise, use of another regimen is recommended.

- *PLHIV on OST:*
  The methadone dose required to prevent the development of opioid-withdrawal symptoms has to be increased as long as EFV, NVP or LPV/r is used *(200–203)*. Caution should be used if the ART regimen is revised and either of these drugs is no longer used, as the patient may then be overdosed with methadone. Buprenorphine is a safer and favoured alternative to methadone in PLHIV on ART.

- *Anticipated low adherence:*
  It is recommended to use PI/r instead of NNRTI to reduce the risk of resistance.

- *Psychiatric disorders:*
  EFV is relatively contraindicated in such situations, and use of another ARV in the regimen is recommended.

- *Major concern with adverse drug reactions:*
  Some PLHIV have an overwhelming fear of developing EFV-related CNS symptoms, which deters them from starting ART. In such situations, use of other regimens is recommended.

4.3. ART adherence

A durable favourable response to ART requires strict adherence to the indicated dosing schedule from day one of ART initiation *(204–207)*. By strict adherence is implied that the total daily intake of the prescribed doses of medicine is maintained at all times. Low or insufficient adherence has consequences for the patients, public health and national economies, as follows.

- PLHIV reduce their future treatment options, as insufficient adherence leads to the selection of virus-carrying, drug-related resistance mutations *(208–210)*. Once a virus has acquired a sufficient number of such mutations to make it non-susceptible to a given drug, it is unlikely that the person will ever again be able to use the drug. When viral resistance mutations appear they often mean that the virus is not just resistant to the drug(s) in the regimen but also to other drugs in the same class (cross resistance), which may further reduce future drug options.
- The selection for resistant viruses leads to increased probability of such viruses being transmitted to other people *(211)*. Transmitted drug resistant virus reduces the choice of active first-line drugs and, if resistance testing prior to ART initiation is not performed, impairs the response to first-line ART.
- The presence of resistant strains will result in increased use of second-line, third-line and salvage regimens, which are in general more expensive than first-line regimens.
- Low adherence also means a higher risk of disease progression *(212,213)*, resulting in higher costs for treating opportunistic infections.

It is the patient's responsibility to ensure reliable intake of the prescribed medication, and it is the responsibility of the provider prescribing the medication to ensure that the patient understands why optimal adherence is critically important, and to provide the necessary support to optimize the chances of full adherence *(214)*.

4.3.1. Barriers to high adherence and counteracting strategies

Health care workers should identify possible factors that might lead to poor treatment adherence and try to address them accordingly (strong recommendation, B).

4.3.1.1. Patient factors and supportive methods

It is the patient who determines when to take the medicine. It has proven impossible to reliably predict who will have suboptimal adherence based on demographic or social characteristics *(215,216)*, and individual adherence rates also vary over time *(217)*. Most PLHIV under treatment will exhibit low adherence at some time.

Barriers to adherence include:

- illicit drug *(218)* and alcohol use (may impair regular intake of all medication)
- poor diet
- religious beliefs *(219)*
- fear of disclosing HIV status through routine medications
- fear of adverse drug reactions and doubts about the necessity of medication *(220)*
- psychiatric conditions, including depression *(221)*
- lack af access to ART (including difficulty accessing health care service)
- pill fatigue
- incarceration *(222)*.

Methods to support adherence include:
- ongoing education on ART and adherence
- prompt response to patients' misconceptions
- regular evaluation of patients' commitment to ART
- peer interventions
- regular assessment of mental health problems
- assessing behavioural skills needed for adherence
- contacting specialized social care services and other institutions.

4.3.1.2. Provider factors

Health care providers should clearly understand adherence and its role in the development of resistance when providing adherence support. Professionals working in the area of HIV/AIDS require continuous education in adherence issues. There are several strategies that health care workers should apply to increase adherence.
- Every HIV treatment centre should have a written and regularly reviewed adherence strategy.
- Health professionals need to be engaged in multidisciplinary adherence support programmes *(223)*.
- Exploring patient preferences for involvement may act as a catalyst to adherence.
- Adherence services should be offered to all PLHIV, taking into account the varying degrees of adherence that they all show over the course of treatment.
- Adherence support should be continued for second-line and salvage regimens. Viral failure usually reflects poor adherence, and hence is a key point for reinforcing the requirements for adherence and support interventions *(224)*.
- As maintaining optimal adherence is a continuous process and not a single event *(225)*, support must be offered when starting ART, changing ART and as a part of routine follow-up.
- Providers must ensure that PLHIV have sufficient understanding of HIV, the relationship between adherence and resistance and potential adverse drug reactions. Verbal information should be supported by written information.
- Pill diaries, pill charts, medication containers, electronic reminders and enlistment of family and friends as reminders can all be recommended *(226)*.
- Adherence to ART is improved where PLHIV view their relationship with their doctor and other health care providers positively *(227)*.
- Early follow-up (e.g. via telephone) should occur two days after initiating or changing a regimen, to evaluate whether the patient needs more information or has unregistered problems.
- When interviewing PLHIV about adherence, encourage dialogue and use open-ended question (e.g. "Please tell me how you have teken the medication during the past week?")
- Partnership between clinics and community-based organizations can improve the uptake of information, especially among hard-to-reach populations and some ethnic groups.
- Continuous access to ART should be provided to the patient at all times once initiated.

4.3.1.3. Regimen factors and strategies

- Dosage more than BID is associated with lower adherence levels *(228)*, while there is probably no major adherence difference between BID and QD dosing *(229)*. However, some PLHIV's lifestyles may minimize adherence under BID, so QD is the preferred method for them.
- A low pill burden is associated with a better chance of optimal virological response to ART *(230)*.
- Adherence levels are not correlated to any particular class of ARVs. However, conflicting dietary rules for different drugs can be a problem *(231)*.
- Harmful drug interactions and adverse reactions can influence adherence. Patient expectations that a drug may cause discomfort can be a barrier. Doses can be missed due to vomiting or diarrhoea, and fatigue can cause sleeping past doses *(232)*.

Methods to support adherence include (233):

- adjusting the regiment to lifestyle patterns such as eating, sleeping and working;
- assessing individual preferences for pill size, formulation, burden, dietary restrictions, etc.;
- showing PLHIV the pills prior to regimen selection;
- educating about adverse reactions prior to prescribing a drug (type of reaction, when it may emerge, the potential for reversibility with continued intake, how to reduce symptoms, how to react if drug reactions occur (i.e. contacting the treatment centre for advice, never ceasing the regimen without prior consultation with the treatment centre, etc.).
- dispensing medication in small amounts at frequent intervals once ART is first initiated, which can facilitate opportunities to address adherence problems before they lead to resistance;
- limiting treatment disruptions and misuse;
- utilizing QD options and FDCs *(234)*, which can lower the pill burden and be beneficial early in treatment;
- using directly observed treatment (DOT) *(235,236)*, particularly in hospitals and among drug users;
- addressing lifestyle barriers to adherence (social and psychological support, psychiatric disorders *(237)*, OST *(238)*, disulfiram) and
- Contacting patients regularly *(239)*.

4.4. ART success and failure

All PLHIV should be regularly monitored by skilled health care professionals supervised by experts in HIV care. Ideally all PLHIV on ART should have access to both immunological and virological tests. Successful ART can be defined by virological, immunological or clinical criteria (see Table 8).

Table 8. Criteria for treatment success

	Virological		**Immunological**	**Clinical**	
Marker	Viral Load (VL)		CD4 cell count	WHO Clinical stage	Tolerability
Time[a]	24 weeks [b]	48 weeks[b] and thereafter	24–48 weeks and thereafter	By 12 weeks of treatment initiation should be asymptomatic or have few symptoms [c]	Continued assessment
Suggested targets[a]	<200 copies/ml	<50 copies/ml	Increase from time of initiation of ART by at least 50 cells/ mm^3	Stage 1 or 2[c]	No clinical adverse drug reactions (nor subclinical emerging to become clinical at some point in time) should be present 3 months after initiation of an ARV drug

[a] Time of evaluation relative to time of initiation of ART – numbers indicate suggested ranges only.
[b] VL levels should decrease gradually – for most patients, except those with high VL's prior to initiation of ART, the VL should be < 50 copies/mL already by week 24 or if not <50 copies/ml should show a significant downward trend towards <50 copies/ml by week 24.
[c] Please see section II.5.3 below for more information on immune reconstitution inflammatory syndrome (IRIS).

Failure of an ART regimen implies that the person treated experiences a suboptimal response relative to what is expected (see Table 8) or experiences treatment-limiting adverse drug reactions that prevent the regimen from being continued (irrespective of whether the response was optimal or not in other ways). These concepts are critical to all health professionals involved with the care of PLHIV, as they indicate the rational choices of when to replace components of ART, and their assessment should thus be an integral part of the care provided (see II.5).

There are three ways of assessing ART response: clinically, immunologically and virologically. As the immediate aim of ART is to prevent HIV from replicating, the virological response criterion is the most direct and sensitive indicator of success or failure. Although less specific, many health professionals nevertheless use the immunological and clinical criteria instead, since the technology required to measure the VL is not available throughout the WHO European Region. Randomized controlled trials *(240,241)* have shown that monitoring of ART by clinical assessment alone leads to excessive risk of mortality, HIV disease progression and unnecessary switches of ART for patients with an optimal virological response (See Table 8), although ART still provides substantial benefit in this context.

4.4.1. Virological response and failure

- VL is the earliest indicator of a response to ART, as levels will decrease 1–2 $\log_{10}$ copies/mL as soon as 2–4 weeks after ART initiation in adherent PLHIV.
- Failure of the VL to fall below <200 copies/ml by week 24 of treatment or <50 copies/ml by week 48 indicates virological failure. It takes a longer time to achieve a VL < 50 copies/mL if the VL prior to initiation of ART was high; however, by 48 weeks after ART is started, all PLHIV on effective ART should have VL <50 copies/mL (15).
- Once the VL criteria have been achieved, if two subsequent VL measured at least two weeks apart, are >200 copies/ml while the patient is still taking ART, this implies virological failure in the form of virological rebound *(242)*.
- If no interventions are implemented, and ART is merely continued in PLHIV experiencing virological failure, there is a large risk that HIV may gradually acquire (if it has not already) drug resistance mutations *(210;243–245)*. Conversely, as long as the VL is < 200 copies/mL, HIV appears not to accumulate mutations *(246)*.
- "Blips" are single slight elevations of VL, from under the quantification n threshold (e.g. of 50 or 400 copies/mL) to levels < 1000 copies/ml *(247,248)*. They may occur without the development of resistant virus strains *(248),* but should be an indicator for a discussion of adherence *(248)*. In such situations, the VL should be checked again after 2–4 weeks.
- Optimal changes in VL levels over time should be used as positive reinforcement in the adherence counselling, whereas suboptimal changes provide a clear and compelling argument to carefully review this adherence (see II.4.3) *(249)*. There may be other explanations for virological failure than poor adherence, including laboratory errors, transmitted drug resistance and drug-drug interactions.
- If there is no obvious reason for virological failure, and/or adherence interventions have been applied, a second-line regimen should be considered *(250)* (strong recommendation, B).

4.4.2. Immunological response

- CD4 cell count response on its own is a reasonable marker of ART success.
- On average, the CD4 cell count increases by about 150 cells/mm³ in the first year after providing ART initiation *(251,252)*. Failure to increase CD4 cell count more than 50 cells/mm³ after the first year of ART is considered immunological failure. Factors associated with suboptimal immunological response include virological failure, age and medication (ZDV *(253)* and the combination of ddI + TDF) *(137–140)*.
- In situations of immunological failure but with an optimal virological response (see above), there is no strong evidence that changing ART or reinforcing the notion of adherence will improve the clinical outcome.
- Conversely, only in settings where VL monitoring is not available as part of routine care should adherence be reassessed and ensured and a second-line be considered for patients experiencing no increase or – more significantly – a decline in their CD4 cell count to low levels.

4.4.3. Clinical response

PLHIV suffering from HIV-related conditions usually become asymptomatic (stage 1) or have minimal or minor HIV-related signs and symptoms (stage 2) weeks to months after ART is initiated. Some WHO clinical stage 3 or 4 OIs can recur despite successful use of ART, e.g. as part of an IRIS *(254–258)*. Also, it takes time for treatment with ART to result in effective immune system recovery. In particular

in the first year after starting ART, patients with good virological responses may still develop OIs. However, a new or recurrent WHO clinical stage 3 or 4 event (OI or other HIV-related illness) after initiation may also be an indicator of suboptimal response to ART, and thus it is critical to assess whether the occurrence of the OI is linked with virological failure. If so, the treatment should focus on managing the OI and the underlying HIV infection, whereas only the OI has to be managed in patients with virological success. In settings without access to such laboratory assessments, it is not possible to make this distinction; often, the emergence of an OI will lead to a switch of the ART from first to second-line. Although this is a recommendable approach, it will nevertheless lead to many unnecessary switches of ART *(240, 259–261)*. Therefore, it is recommended, if at all possible, to measure both CD4 cell count and VL of PLHIV on ART who develop OIs (strong recommendation, B).

4.4.4. Dissociation between virological and immunological response criteria

In some PLHIV with virological failure, the CD4 cell count can remain stable or increase for a period of time *(262–264)*. In such situations, the presence of virological failure should take priority and guide the decision on switching ART. Conversely, this situation may be misinterpreted as successful ART if the response is only monitored by CD4 cell count and not VL. It is therefore recommended that one measure VL at regular intervals in all PLHIV receiving ART (strong recommendation, A).

4.5. Second-line ART regimen

- When a PLHIV has experienced a suboptimal response to a first-line ART regimen, and the reasons have been investigated and addressed to the extent possible without reversing the situation, it is recommended that all components of the ART regimen be switched (i.e. the patient be provided with a second-line regimen) *(265)*.
- Second-line ART is the next regimen used in sequence immediately after first-line ART has failed. The PI class is preferentially reserved for second-line use in settings using a public health approach. Ideally, ritonavir-boosted PIs are recommended, supported by two NRTIs.
- It is recommended that a resistance test be performed prior to the switch while the patient remains on the first-line ART regimen, and that the the second-line regimen comprise drugs from at least two classes that would be expected to be effective based on the resistance test results (strong recommendation, B).
- In health systems without resistance testing facilities or the ability to perform timely resistance assessment, specific recommendations are provided in Table 9 depending on type of first-line regimen that is failing (strong recommendation, B).

4.5.1. NRTI component considerations

- Minimum changes for a second-line regimen are one or two new NRTIs, as indicated in Table 9.
- The recommendations for the second-line NRTIs are driven primarily by knowledge of which types of resistance-related mutations the various drugs may be selected for. Other combinations than those in Table 9 maybe suboptimal or even antagonistic, and are not recommended without consultation with an expert.
- If the first-line regime consisted of a thymidine analogue, TDF (preferred) or ABC (alternative) is recommended. Conversely, if the first-line regime consisted of a non-thymidine analogue, then either ZDV in combination with ddI or 3TC is recommended, with d4T being an acceptable choice.
- If 3TC or FTC was part of the first-line regimen, some recommend continuing it in the second line regimen, despite the likelihood that the virus will have acquired resistance. There is some evidence that maintaining 3TC is associated with virological and clinical benefit despite HIV having acquired resistance it *(266,267)*, whereas it is unlikely that its continued use help the second-line regimen to regain complete viral control *(268)*. An alternative recommendation is to replace 3TC or FTC with either ETV or RAL.

Table 9. Recommended second-line ARV regimens after experiencing virological failure on indicated first-line regimen and with no access to timely results from a resistance test to guide the choice [a]

Failed first-line regimen	Second-line regimen					
	Preferred		Alternative		Acceptable	
	NRTI	3rd drug	NRTI	3rd drug	NRTI	3rd drug
ZDV or d4T + 3TC or FTC + (EFV or NVP)	TDF+ 3TC or FTC [b]	LPV/r [c] or ATV/r	ABC + 3TC or FTC [b]	DRV/r [c]	ddI + 3TC or FTC [b]	FPV/r or SQV/r
TDF or ABC + 3TC or FTC + (EFV or NVP)	ZDV+ ddI	LPV/r [c] or ATV/r	ZDV + 3TC or FTC [b]	DRV/r [c]	d4T + 3TC or FTC [b]	FPV/r or SQV/r
2 NRTI+PI/r	As above	DRV/r [c]	As above	LPV/r [c]	As above	RAL
2 NRTI + RAL	As above	LPV/r [c] or ATV/r	As above	DRV/r [c]	As above	FPV/r or SQV/r
3 NRTI	As above	LPV/r [c] or ATV/r	As above	DRV/r [c]	As above	FPV/r or SQV/r

[a] Performing a resistance test and receive the results in a timely way is strongly recommended; the results from this test should be used to guide the choice of the second-line regimen.
[b] 3TC or FTC is maintained despite prior failure. This is a controversial recommendation, as some experts would favour composing the second-line regimen with three fully active drugs, and such as ETV or RAL. There is some evidence that maintaining 3TC is associated with clinical benefit despite HIV having acquired resistance to it *(266)*.
[c] LPV/r is listed as the preferred and DRV/r as an alternative RTV-boosted PI in this table due to cost considerations and since DRV/r should be preferentially used as part of salvage ART. DRV/r is dosed as 800/100 mg QD in PI-naïve PLHIV and as 600/100 mg BID in PLHIV having experienced virological failure to a PI-based ART regimen.
(For recommended dosages of ARVs, please refer to Annex 5).

4.5.2. PI component considerations

- With a first-line regimen containing an NNRTI, it is recommended to use a PI/r as part of second-line ART. ETR may be considered if resistance tests suggest that the virus remains susceptible to it, but the drug should be combined with a PI/r in the second-line regimen *(269)*.
- The differences among the PIs lie in the number of mutations needed to develop resistance, the profile of their side-effects, pill burden, daily dosing and cost.
- One of the highest genetic barriers for resistance is documented for DRV/r and slightly less so for LPV/r *(270)*.
- The resistance profiles of ATV/r, FPV/r and SQV/r show slight differences with little or no clinical impact as second-line regimens.
- Possible side effects, comorbidities, drug interactions and individual preferences should influence the choice of PI.
- If first-line ART regimens containing PIs fail, the choice of second-line regimens should be based on the resistance profile. If a resistance profile is not available, then resistance to the PIs contained in the first-line regimen must be assumed to be the cause of the regimen's failure (see II.4.4 above).
- LPV/r or ATV/r are the PIs of choice as part of second-line ART (moderate recommendation, A). If patient is suspected or known to harbour HIV with transmitted or acquired PI drug-related mutations, DRV/r is the preferred PI/r (strong recommendation, A).

4.6. Salvage regimens

If failure of second-line ARV treatment occurs (using virological, immunological or clinical criteria), a salvage regimen should be considered. Salvage regimens are combinations of drugs that will probably work even against viruses that are partly drug resistant. Every regimen after second-line treatment is complicated and requires a high level of ART knowledge and skill. Performing a resistance test in these circumstances is highly desirable. It is at times better to wait for the resistance test to become

available before initiating salvage treatment, although this strategy can be dangerous, particularly if the CD4 cell count is low.

- If possible, two or three effective drugs should be used, preferably from new classes, for example DRV/r, RAL or ETV *(156,157,271–275)* and the NRTI combination should be optimized if possible. This will lead to renewed and durable virological success in most PLHIV provided that adherence is optimal.
- The genetic barrier of DRV/r seems to be even higher than that of LPV/r, and data show its efficacy to be comparable or better than that of LPV/r *(270)*.
- RAL should only be used if combined with other active drugs *(276–278)*. RAL should not be considered a suitable replacement for a PI/r in advanced HIV treatment *(279)*.
- ETV is also potentially useful, although HIV may have already acquired cross-resistance between ETV and EFV and/or NVP if these drugs were used earlier in course of treatment *(269)*.
- Another drug to consider is MRV if the patient's HIV virus is CCR5-tropic *(280)*. ENF was used previously, but is difficult to administer and costly.
- When composing salvage regimens, combinations of two or more PIs (other than /r) *(281)*, two or more NNRTIs or more than 3 NRTIs should be avoided.
- All effective therapeutic options might be exhausted in some PLHIV, and no combination will be able to provide durable virological success. In such cases, further attempts to find better combinations should be made, to improve immunological and clinical targets as opposed to virological suppression. ART should not be stopped in these circumstances *(282)* as some residual benefit in terms of prevention or slowing of falling CD4 cell counts is likely to be present (see below).

4.7. Structured treatment interruption

Before 2006, there was a fairly relaxed attitude toward temporarily interrupting ART in patients with high CD4 cell counts, and accepting temporary interruptions in case of patients undergoing surgery or due to other short-term disturbances in normal living. However, in 2005–2006, several studies emerged to demonstrate that interruption of ART leads to excess risk of HIV clinical disease progression, increases the risk of other serious organ diseases and selects for ART resistance irrespective of whether there had been a full or only partial virological response *(282–288)*. Therefore, structured treatment interruption is not recommended; patients should be carefully instructed to ensure that they are responsible for having a sufficient quantity of medicine available to continue on ART without interruption at all times (strong recommendation, A).

The only clinical situation where it remains controversial to continue ART is for women who initiated ART during pregnancy with CD4 cell counts above the currently recommended thresholds for initiation. However, many experts would continue ART also after the pregnancy has ended except if the woman had very low VL and high CD4 cell counts before ART was initiated (moderate recommendation, B).

If a PLHIV, for whatever reason, is to stop ART, it should be done under the supervision of the health care provider to ensure safety. If the regimen includes an NNRTI, it is recommended to use either of the following two strategies *(289)* aimed at reducing the risk of selection of NNRTI resistance (which hampers the ability to achieve durable virological response once the NNRTI-based regimen is reintroduced) (moderate recommendation, B):

- a staggered approach, where the NNRTI is stopped one week before the NRTIs. The risk of NNRTI resistance development remains after using this approach, although probably at a lower level.
- a sequential approach, switching the NNRTI to a PI/r three weeks before stopping all ART.

If the PLHIV is chronically infected with HBV, re-emergence of HBV replication potentially leading to liver impairment may occur if ART containing anti-HBV drugs is interrupted *(290–293)*.

Once ART has been interrupted, HIV disease progresses faster than in PLHIV who have not yet initiated ART and for whom it is not needed yet. The VL increases within the first 4–6 weeks from the time of interruption and the CD4 cell count declines within the first 3–8 months to levels present prior to commencing ART. The time line of HBV-DNA in chronic HBV-coinfected PLHIV is comparable *(293)*. Interruption may also lead to clinical symptoms of primary HIV infection and thrombocytopenia *(294,295)*. PLHIV interrupting ART should be seen at least every two months after interruption and ART should be reinitiated as quickly as possible (strong recommendation, A) preferably after results of a resistance test to ensure that the virus is susceptible to the chosen regimen.

5. Clinical monitoring of PLHIV

Once a person has been diagnosed with HIV infection, a continuum of care and monitoring should be ensured.

5.1. Monitoring of laboratory indicators before ART

- CD4 cell count
  - The CD4 cell count provides an impression of the extent of immunodeficiency. The lower the number, the higher the risk of OI. Most OIs in a population of PLHIV occur among those with a CD4 cell count < 200cells/mm^3, although some OIs (TB, recurrent bacterial infection, Kaposi's sarcoma and certain types of lymphomas) may also frequently occur in those with CD4 cell counts in the 200–300 cells/mm^3 range.
  - Measurement of the CD4 cell count is associated with significant variability, and it is recommended to repeat the measurement before clinical action is taken, and to assess trends over time to better identify outliers.
  - If ART initiation is under consideration (i.e. CD4 cell count is around 400–450 cells/mm^3), CD4 cell count should be monitored every three months. The median average loss is 50 CD4 cells/mm^3 per year, but there is marked variability among patients and CD4 cell counts can drop very quickly, especially with concomitant infection or in case of high viral load.
- Viral load
  - In PLHIV not yet started on ART, regular VL monitoring provides an implication of the degree of viral replication in the body, and there is an association between the VL and subsequent risk of CD4 cell count decline. The VL tends to remain relatively stable after acute infection is resolved, with a trend towards a gradual increase as the immunodeficiency accelerates *(53,296)*. Untreated PLHIV with CD4 cell counts above 500 cells/mm^3 usually have VLs in the range of 5000–50 000 copies/ml, whereas those with CD4 cell counts below 350/mm^3 have VL's in the range of 50 000–500 000 copies/ml *(53)*. Some variability in VL measurements exists, but it is rare to observe fluctuations in levels in untreated individuals exceeding 1 $\log_{10}$ copies/ml over a 12-month period.
  - PLHIV with higher VL (>100,000 copies/ml) should be monitored (clinical and CD4 cell count) more intensively than PLHIV with low VL (< 5,000 copies/ml) (e.g. every three and six months, respectively).
  - VL testing is expensive to perform. If resources are limited, priority should be given to use the VL resources on PLHIV receiving ART.

The general laboratory testing panel (see Table 3 above) should be repeated every six months unless the patient initiates ART or other clinical circumstances (comorbidities, pregnancy, etc.) change.

5.2. Monitoring of laboratory indicators of ART patients

ART consists of drugs that can inhibit HIV replication. Successful ART is first reflected by a decrease of VL with secondary immunological responses resulting from reduction in viral replication occurring later. ART efficacy is preferably monitored by sequential VL measurements; assessment of CD4 cell count provides an independent way to assess benefit, as well as allowing for evaluating contemporary risk of OI.

Although relatively expensive, routine VL evaluation is recommended to be introduced as part of ART monitoring for several reasons:

- it identifies the subgroup for whom ART is not working optimally, allowing the health system to focus on this smaller group requiring additional interventions;
- it reinforces counselling on proper adherence;
- it reduces the risk of gradual accumulation of resistance mutations among PLHIV experiencing virological failure;
- it reduces the risk of unnecessary switches to more costly second-line regimens;
- provided that the health system is able to appropriately manage PLHIV with virological failure (see II.4.5 and II.4.6), regular VL monitoring will reduce the size of the population with transmittable HIV in general and HIV with drug resistance mutations in particular *(240,297)*, and hence
- it will assist in maintaining the currently recommended first-line regimens as the appropriate choices *(211)*.

These benefits are, however, only fulfilled if the interval between drawing blood and obtaining results is reasonable (response time < 4 weeks) and the quality of storage and shipment of the sample and the laboratory assays meet international standards. If laboratory assessment is not accessible, ART can still be used. In such situations, clinical symptoms and signs are used to determine whether viral failure or drug intolerance are present *(240)*. Although this strategy is associated with excess morbidity and mortality, the benefits of using ART still clearly outweigh the additional risks.

Table 10 outlines recommendations for laboratory assessment after ART is initiated (moderate recommendation, B). Of note, the frequency varies depending on type of ARV's used and presence of viral hepatitis coinfection. The recommendation assumes that the person using ART is asymptomatic.

Table 10. Frequency of laboratory testing, generally and with specific ARV use, in PLHIV initiating ART

	Time from ART (or a given drug) is first initiated							
	Just prior to	**Week 2**	**Week 4**	**Week 12**	**Week 24 and 36**	**Year 1**	**Every 3-6 months thereafter[a]**	**Every year**
VL	X		(X)	(X)	X	X	(X)	X
CD4 cell count	X		(X)	(X)	(X)	X	(X)	X
Complete haematological assessment	X		X	X	(X)	X	(X)	X
Liver Function Test (LFT)[b]	X	X (NVP)	X	X (NVP)	X (NVP)	X	(X)	X
Cholesterol triglycerides	X					(X)		(X)
Renal function test	X	X (TDF)	X	X		X	(X)	X

X: laboratory tests to be performed irrespective of the ARVs being administered; X (ARV): laboratory tests to be performed if an ARV in parentheses is being administered; (X): optional test.

[a] After two years of follow-up without evidence of virological failure, the interval between clinical and VL (and possibly CD4 cell count) monitoring can be extended to 6 months thereafter.

[b] LFT should be done at all visits for PLHIV with impaired liver function or PLHIV chronically coinfected with HBV or HCV.

5.3. Immune reconstitution inflammatory syndrome (IRIS)

IRIS may occur in the first weeks after initiating ART, more often in PLHIV with CD4 cell counts <100 cells/mm^3 *(98,99,254–258,298)*. IRIS develops because of the existence of an infection, where initiation of ART may lead to an inflammatory reaction due to an improved and activated immune system. The infection may be dormant, and the IRIS results in the infection being clinically recognizable or the infection may already have caused clinical symptoms and the IRIS leads to paradoxical reactions (i.e. worsening clinical symptoms despite effective management of the infection). IRIS may occur in up to a third of people with TB who initiate ART but is not a reason for deferral. Indeed recent studies in PLHIV with low CD4 cell counts have demonstrated a survival benefit of starting ART two weeks after the initiation of TB treatment *(101)* (See also Protocol 4, *Management of tuberculosis and HIV coinfection (in press)*. The IRIS often presents with symptoms that differ from those usually seen with the infection, for example, in abscesses with *Mycobacterium avium complex* (MAC) or curious chest X-rays with PCP. TB, MAC, CMV and *Cryptococcus* are the most common OIs implicated in early IRIS, but worsening of a treated PCP or even Kaposi's sarcoma may also occur.

It is sometimes difficult to disentangle the reasons why a PLHIV who recently initiated ART clinically deteriorates. The differential diagnoses are wide and include IRIS as well as adverse drug reactions or lack of efficacy of either ART or of drugs used to treat a concomitant infection. Knowledge of the adverse effects profiles of medications used combined with information from relevant laboratory analyses (organ function tests and antimicrobial resistance tests) are required to help identify the cause of clinical deterioration. IRIS in principle reflects that ART is working as intended, and ART should be continued along with treatment of the OI. Low-dose prednisone or prednisolone (20–60 mg/d) may dampen IRIS symptoms.

5.4. Monitoring adherence

Every patient's adherence to ART should be measured and recorded during routine clinical visits (see II.4.3). While there are different tools for monitoring adherence (see Annex 7), the preferred method is recording the quantity of drug pick up or the completion of a standardized questionnaire for the week before the visit. Virological failure should always prompt physicians to discuss adherence behaviour with their PLHIV. Optimizing adherence in the first four to six months of treatment is crucial to ensuring long-term success of the ART.

Staff should provide individualized support to adherence, based on the needs of each patient at any time during treatment. At every patient visit, health care providers have to make sure that every patient:

- has emotional and practical living support
- fits the drug regimen into a daily routine
- understands that non-adherence leads to resistance
- recognizes that all doses *must* be taken
- feels comfortable taking drugs in front of others
- keeps clinical appointments
- understands ARV interactions and side-effects
- knows alarm signals and when to see a doctor about them.

Once a patient is on ART, additional issues may arise which also need to be addressed in a timely fashion:

- treating depression to enhance adherence and improve long-term outcomes;
- management of drug interactions and dosages;
- providing additional monitoring and support during periods of instability in patients with drug and alcohol dependence; and
- nausea in pregnant women (see Protocol 10 *Prevention of HIV transmission from HIV-infected mothers to their infants (in press)*.

5.5. Management of ARV adverse drug reactions

Adverse drug reactions are common with ARVs and need to be effectively managed (see Table 11). They can be divided into categories according to:

- time of onset – early (within the first weeks) or late (after several months or even years of use);
- frequency – frequent (>10% develop the reaction), common (2–10%) or rare (< 2%);
- severity – life threatening, severe, moderate, or mild; and
- spontaneous reversibility – yes (reduced symptoms despite continued use of the ARV), no (once manifested, only discontinuation of the drug will remove the reaction); and
- required discontinuation – yes (non-reversible reactions irrespective of severity, as well as severe reversible reactions) and no (mild or moderate reversible reactions).

Management of adverse drug reactions should follow the following principles:

- Prior to starting on ART, the PLHIV should be informed about the adverse drug reactions that may occur and how to react to them. It is essential that the patient can get in contact with a competent health care professional at all times, in particular in the first few weeks after ART is initiated.
- If an adverse drug reaction develops, it should be classified according to severity and the potential for reversibility. Regimens should be switched for patients with treatment-limiting reactions, and those who do not fall into that category should be reassured and carefully monitored.
- Pre-emptive switches of ARVs (i.e. in asymptomatic patients at risk of developing adverse drug reactions) should be considered if the patient receives one or the more toxic ARVs (e.g. d4T, ddI, IDV) or laboratory or clinical assessments suggest that an adverse drug reaction is emerging and will likely cause clinical symptoms or irreversible damage to organ function. Of note, pre-emptive switches are only relevant to consider provided that safer alternatives with comparable virological efficacy are available.
- Drugs of the same class should preferably be substituted for those provoking the adverse reactions.

Table 11. Documented toxicity of ARVs and suggestions for management

ARV	Toxicity	Management
Bone effects (osteopenia and osteoporosis)		
TDF Possibly other ARVs	• TDF reduces bone mineral density early on (osteoporosis develops in older PLHIV, particularly in women, but also men with hypogonadism, high dose steroid users and PLHIV with vitamin D deficiency) • Takes years to develop	• Monitor symptoms and LFT's. If isolated alkaline phosphate elevation, explore possible vitamin D deficiency; if found, provide vit D replacement therapy. • In PLHIV at risk of osteoporosis, consider screening for low mineral density according to guidelines in general population; ensure sufficient dietary calcium and vit D, and if spontaneous fractures, or evidence of osteoporosis, consider bisphosphonate therapy. • consistent scan, if available
Bone marrow suppression including anaemia and neutropenia		
ZDV	• Anaemia and neutropenia, (slight decrease is normal with ZDV) • 1–4%, dose dependent • Usually within first 4 weeks, but may occur later if ZDV is combined with drugs for other conditions that may cause bone-marrow suppression (e.g. chemotherapy)	• Monitor blood count after 2, 4, 12 weeks. Macrocytosis with mild anaemia is common and usually do not require intervention. • Change ZDV to another NRTI (TDF, ABC or d4T); erythropoetin should not generally be used.

ARV	Toxicity	Management
Cardiovascular system effects		
PI/r ABC	• PIs may cause increased total cholesterol (TC), HDL and LDL-cholesterol and triglyceride levels (d4T may also cause TG elevation as consequence of adipocyte toxicity). • PIs may elevate risk of ischaemic heart disease (IHD), as may ABC. This effect is primarily of clinical relevance for PLHIV at elevated underlying CVD risk (use Framingham or other risk calculators to calculate underlying risk). • It develops after months to years of therapy.	• Monitor fasting lipid levels at initiation of ART and every year. • Encourage low saturated fat diet, exercise & smoking cessation. Treat hypertension, diabetes mellitus and dyslipidaemia according to guidelines in general population (do not use simvastatin with PI/rs, start with lower doses of other statins and gradually dose escalate to desired lipid effect (obs adverse reactions). Use acetylsalicylate only if patient has history of CVD.
Central nervous system (CNS) effects		
EFV	• Drowsiness, sleep disturbances, impaired concentration, exacerbation of pre-existing psychiatric disorders • More than 50% • Develops after first dose; symptoms gradually subside over days to a few weeks in most PLHIV.	• Warn patient, take psychiatric history, refer to psychiatric consultation. • Discontinuation is usually not necessary. Residual less intense symptoms may persist and warrant considerations for switching at a later time.
Gastrointestinal intolerance		
LPV/r, FPV/r, SQV/r ZDV, ddI	• Nausea and vomiting (ZDV), loose stool/ diarrhoea (PIs and ddI) • Common • Develops after first dose. ZDV reaction is usually reversible, whereas drug-induced loose stool is not.	• Rule out other reasons (GI coinfection, ulcers). • Treatment is loperamide if other causes for loose stool are ruled out and consider switching the causative ARV; metoclopramide, ondansetron for nausea and vomiting.
Hepatic necrosis (life-threatening)		
NVP	• Fever, rash (50%), nausea, vomiting, eosinophilia, elevation of ALT/AST • 1–2% of all NVP treated individuals, higher if CD4 cell count >250 in females and >400 in males • Usually in first 12 weeks, rare after 24 weeks	• Monitor LFT at weeks 2, 4, and 12, and then every three months. • Hepatic necrosis is life threatening; in severe clinical situations, stop all drugs immediately. • Treat the liver failure with standard interventions.
Hepatotoxicity (usually indicated by elevation of LFT)		
NRTIs (ddI) NNRTIs (NVP) PI (ritonavir, TPV) MRV	• Otherwise unexplained elevation of LFT • 8–15% with NNRTI; lower for PI • More frequent in PLHIV with underlying liver disease, chronic HBV or HCV, chronic alcoholism or use of other hepatotoxic drugs (e.g. rifampicin) • Develops after days to weeks (NVP) or weeks to months (other drugs), years for ddI (non-cirrhotic portal hypertension)	• Monitor LFT's regularly. • Elevation often resolves with continuation of NNRTI or PI. • If severe or not reversible, switch NNRTI to PI/r.
Hypersensitivity (life threatening, in case of re-exposure: anaphylactic shock)		
ABC NVP	• Fever and rash, plus fatigue and nausea • 5% (>50% in persons that are HLA B*5701 pos), • Rare after six weeks	• Monitor skin for rash, do not start these drugs together with other rash-producing drugs. • Stop ABC, do not use again if diagnosis is firmly suspected. • ChangeABC to TDF, ZDV, or d4T.

ARV	Toxicity	Management
Icterus (isolated hyperbilirubaemia)		
ATV IDV	• Elevation of unconjugated bilirubin without changes in LFT's (is harmless; possible itching, no liver damage, reversible) • 5% (most PLHIV on ATV have bilirubinaemia) • Develops within first days to weeks of therapy.	• Monitor clinical symptoms. • Switch drug only if not tolerated to other PI/r.
Insulin resistance and diabetes mellitus		
d4T ZDV IDV	• Impaired glucose tolerance, elevated glucose with morning fasting • 1-5% • Develops after months of therapy (those with family history of diabetes and PLHIV with intraabdominal fat accumulation are particular risk)	• Monitor fasting blood glucose. • Recommend appropriate diet and exercise, metformin or insulin as appropriate to maintain glucose control. • Change d4T or ZDV to TDF or ABC, and avoid using IDV.
Lactic acidosis (life-threatening)		
From highest to lowest risk: • d4T with ddI • d4T • ddI • ZDV	• Nausea, vomiting, wasting, fatigue, pancreatitis, multiorgan failure, acquired respiratory distress syndrome (ARDS) • 1–10 per 1000 PLHIV/year for ddI and d4T • Usually after months of therapy (in particular in obese women, pregnant women or PLHIV treated with ddI and ribavirin (contraindicated).	• Monitor for symptoms clinically. If suspected, look for early indicators (S-lactate, creatine phosphokinase (CPK), HCO_3). • The treatment for symptomatic lactic acidosis is bicarbonate. • Change to ABC, TDF, 3TC, FTC or use NRTI-sparing regimen.
Lipodystrophy		
Lipoatrophy: d4T ZDV	• Reduced subcutaneous fat throughout the body (most easy to identify in face, buttocks and extremities) • Develops in most PLHIV if treated for sufficiently long time • Usually after months to years of therapy	• Monitor clinically. • Change d4T or ZDV to TDF or ABC; recovery is slow (may take years). If atrophy is irreversible, consider use of injecting fillers.
Lipohypertrophy: PI/r and other ARV's	• Increase in abdominal girth, breast size, or dorsocervical fat pad (buffalo hump) – fat accumulation is disproportionate (separate from obesity) • Rare – develops after months of therapy	• Measure and compare to previous measurements. • Diet and exercise; change to NNRTI if lipohypertrophy is not tolerable; surgery of buffalo hump maybe done (pad usually recurs).
Nephrotoxicity		
TDF IDV ATV (LPV/r)	• Renal failure, Fanconi's syndrome (only TDF) or nephrolithiasis (only IDV or ATV (rare)) • 1% (TDF), 13% IDV, < 0.1% ATV; more frequent in individuals with baseline renal dysfunction • Usually after weeks to months of therapy (nephrolithiasis associated with periods of dehydration)	• Monitor creatinine (increases), phosphate & potassaium (both decrease) and quantify protein in urine (positive). • Change TDF to ZDV, ABC or d4T if Fanconi's syndrome develops or eGFR continuously decrease without other cause identified. • If switch away from TDF is not feasible, consider dose adjustment of TDF (creatinine clearance is needed).

ARV	Toxicity	Management
Pancreatitis		
From highest to lowest risk: • d4T with ddI • ddI • ddI with TDF, • d4T	• Post-prandial abdominal pain, nausea, high levels of amylase or lipase • ddI 1–7%, (in particular if history of pancreatitis, alcoholism, elevated TG, low CD4 cell count); dose reduction of ddI reduces risk • usually after weeks or months of therapy	• Monitor for clinical symptoms. • The symptomatic treatment is pain medication, parenteral nutrition, drug stoppage. • Change to ZDV or TDF or ABC.
Peripheral neuropathy		
ddI d4T (all NRTIs)	• Pain/paraesthesia of extremities • 10–30%, • Develops after months to years of therapy; PLHIV with low CD4 cell count at particular risk (HIV-associated neuropathy)	• Monitor for symptoms and warn patient. • Treatment is switch to another NRTI (TDF, ABC or ZDV), and pain management, or use non-NRTI based regimens.
Rash		
NVP EFV ETV FPV DRV ABC	• Maculopapular rash • 15% NVP,FPV ~20%, ABC 5% • Develops within days or weeks of therapy	• Monitor skin. • Consider whether rash maybe caused by other drugs able to induce rash (e.g. sulfamethoxazole /trimethoprim and other antibiotics). Rashes sometimes resolve spontaneously with continued ART. • Change NVP to EFV or vice versa. If no improvement, switch to PI/r.
Stevens–Johnson syndrome, toxic epidermal necrolysis		
NVP Less with EFV, ETV	• Fever, rash with blistering, myalgia • NVP: 0.3%, EFV: 0.1% • Usually the first days or weeks of therapy (in particular in women)	• Monitor skin. • Administer antibiotics and intensive care of wounds, perhaps in a burns centre. • Change to PI/r

5.6. Drug-drug interactions

In Annex 6, interaction information is provided for drugs recommended in these guidelines for first-line ART regimens, with the exception of the NRTIs, which have a low potential for clinically significant interactions. In addition to the first line drugs, we have included data on etravirine and maraviroc. The tables have been collated from information provided in the European Summaries of Product Characteristics (SPCs). Table 15 gives the absolute contraindications as listed in section 4.3 of the SPC. Tables 16–18 detail pharmacokinetic interactions from section 4.5 of the SPC that may require dose modification or monitoring, or where coadministration is not recommended. For the effect on plasma concentrations, "↑" indicates an actual or predicted increase in at least one pharmacokinetic parameter (AUC, Cmax, Cmin) of the parent drug and/or metabolites and "↓" indicates a decrease. Where the effect on plasma concentrations is unknown, this is shown by "?". For further information visit the drug interaction resource (www.hiv-druginteractions.org).

III. Suggested minimum data to be collected at the clinical level

The suggested minimum data to be collected are important in the development of key indicators on access to treatment and its success, which assist managers in decision-making on ways to strengthen and expand these services to all who need them.

Statistics (http://www.ua2010.org/UNGASS) should be collected at each clinical facility on a regular basis (e.g. quarterly or semi-annually), preferably using a standardized data capture tool such as HICDEP (HIV Collaboration Data Exchange Protocol) *(299)*, comprising the number of PLHIV:

- seen for care at least once in the previous 12 months;
- seen for care who are eligible for ART (CD4 ≤350 cells/mm^3);
- receiving ART;
- receiving first-line ART by end of reporting period;
- switching from first-line ART to second-line ART within last reporting period;
- switching from second-line ART to salvage ART within last reporting period;
- interrupting ART treatment in the last reporting period, with the reason (e.g. death, toxicity/side effects, loss to follow-up, ARVs not available, etc);
- with a CD4 cell count <200 cells/mm^3 initiating ART in last reporting period;
- who were pregnant and initiated ART in last reporting period;
- who presented with TB in last reporting period;
- who died while on ART, including the cause (e.g. HIV-related mortality or non-HIV-related mortality such as accident, overdose or suicide); and
- who died in total, including the cause (as above).

Annex 1. Essential information on personal history of HIV/AIDS treatment and care

Below is a suggested outline of the minimal information that each clinic should record routinely as part of routine care for individual patients. These data can then be the basis for the reporting items outlined in section III above. It is recommended to record the information electronically, using a standardized data capture tool such as the **HIV Collaboration Data Exchange Protocol (HICDEP)** *(299)*, which enables an easier overview and more timely reporting.

Table 12.		Essential information as part of routine follow-up of PLHIV in care							
Visit date	**CD4 cells/ mm³**	**%**	**VL copies/ ml**	**Current ART[a]**	**Date inter-rupting ART[b]**	**Suboptimal adherence (Y/N)? [c]**	**Reason for switching ART[d]**	**Other medication[e]**	**Significant laboratory or clinical events since last visit[f]**

[a] If never started indicate "none"; use abbreviations for drugs as indicated in beginning of this document.

[b] Insert date of interruption of ART, for PLHIV who have previously initiated ART.

[c] Review relevant section of this document (section 4.3) for appropriate evaluation and proposed interventions to optimise adherence to ART.

[d] Indicate reason for switching one or more of the component of ART if this has occurred at a given visit.

[e] Indicate medication administered chronically to manage dependency (e.g. OST), to prevent infection (chemoprophylaxis) or to prevent other comorbidities (e.g. antihypertensive, antidiabetes, antidyslipidaemic, etc).

[f] Indicate if one of more of the following has occurred since last visit: HIV/AIDS related condition, another type of co-morbidity, laboratory signs of organ failure, resistance test, HBV-DNA and HCV-RNA (if applicable), pregnancy.

Annex 2. Revised WHO clinical staging of HIV/AIDS for adults and adolescents

(Interim European Region version for people aged ≥15 years
with laboratory confirmed HIV infection)

Acute HIV infection
- Asymptomatic
- Acute retroviral syndrome

Clinical Stage 1
- Asymptomatic
- Persistent generalized lymphadenopathy (PGL)

Clinical Stage 2
- Angular cheilitis
- Herpes zoster
- Fungal nail infections
- Weight loss – moderate (5-10% of body weight) and unexplained
- Papular pruritic eruptions
- Oral ulcerations – recurrent (two or more episodes in six months)
- Upper respiratory tract infections – recurrent (two or more episodes in any six-month period of sinusitis, otitis media, bronchitis, pharyngitis, tracheitis)
- Seborrhoeic dermatitis
- Oral hairy leukoplakia

Clinical Stage 3
- Acute necrotizing ulcerative stomatitis, gingivitis and/or periodontitis
- Candidiasis – oral and/or pharyngeal, which is either recurrent (two or more episodes in six months) or persistent (> 1 month)
- Chronic diarrhoea (> 1 month) – unexplained
- Haematological abnormalities – unexplained (anamia (haemoglobin < 8 g/dL), neutropenia (neutrophil count < 0.5 x 10^9/L), thrombocytopenia (platelet count < 50 x 10^9/L))
- Persistent fever (> 1 month) – unexplained
- Pulmonary tuberculosis
- Severe presumed bacterial infections (e.g. bacteraemia, bone or joint infection, empyema, meningitis, pelvic inflammatory disease (severe), pneumonia, pyomyositis)
- Weight loss – severe (>10% of body weight) and unexplained

Clinical Stage 4
- Candidiasis – esophageal or of lower respiratory tree
- Cervical carcinoma (i.e. invasive and not only dysplastic)
- Chronic Herpes simplex virus (HSV) (>1 month of ulceration)
- Chronic cryptosporidiosis (> 1 month of diarrhoea)
- Chronic isosporiasis
- Cryptoccocosis – extrapulmonary (incl. meningitis)
- Cytomegalovirus (CMV) – retinitis, colitis or esophagitis
- Extrapulmonary tuberculosis (excluding lymphadenopathy)
- HIV-associated nephropathy
- HIV encephalopathy
- HIV wasting syndrome
- Kaposi sarcoma and HIV-related malignancies
- Leishmaniasis – disseminated
- Malignant lymphoma – primary brain or B-Cell non-Hodgkin
- Mycobacteria other than tubercle bacilli (MOTT) – disseminated
- Mycosis (e.g. candida, coccidomycosis, histoplasmosis) – disseminated
- *Pneumocystis jirrovecii* pneumonia
- Progressive multifocal leukoencephalopathy (PML)
- Toxoplasmosis – central nervous system including retinal
- Septicaemia with non-typhoid *Salmonella spp.* – recurrent
- Severe presumed bacterial pneumonia – recurrent (two or more episodes within one year)
- HIV-associated cardiomyopathy

Modified from: *(http://www.euro.who.int/__data/assets/pdf_file/0007/78559/E87956.pdf)*

Annex 3. Resistance tests

Resistance testing can only be performed if the plasma sample contains a minimum of 500–1000 copies/ml of HIV-RNA.

Genotypic resistance testing is based on the analysis of RNA mutations. The amplified genome is sequenced. Known mutations are encoded for changed susceptibility of the virus. It is an indirect proof of drug resistance. The resistant virus population has to be higher than 20% of the whole population to be detectable; minority populations of viruses which may carry drug resistance are thus not detected, but can nevertheless result in virological failure *(300-302)*.

The interpretation of the consensus sequences from the genotypic resistance tests is usually based on computer-based algorithms (see e.g. (http://hivdb.stanford.edu/; http://www.hivfrenchresistance.org/) or (http://regaweb.med.kuleuven.be/software/rega_ algorithm/). These algorithms are freely available, and have been shown to guide a rationale choice of drugs to use to compose a virologically effective ART regimen.

Phenotypic resistance testing, like microbiological susceptibility testing, examines the ability of viruses to replicate in cell culture in the presence of different agents. It is compared to the same ability of wild-type virus. The 50% inhibitory concentration (IC_{50}) is a marker of viral susceptibility to drug. The results of the test show different grades of susceptibility.

Which resistance test to use?

All tests are expensive. The time between taking the sample and achieving results can be weeks. Basic genotypic testing should show enough evidence for further planning of regimens. First- and second-line regimens do not require the more expensive phenotypic test. All virological laboratories performing resistance testing for routine clinical use should participate in a proficiency testing procedure to optimise the quality of the test; they should also streamline their routine procedure in order to be able to report the result of their test to the clinician within four weeks of sampling.

Which samples should be considered for resistance testing?

A sample should be sent for resistance testing when a PLHIV first enters care (to optimize chances of detecting transmitted drug resistance), in some settings at time of first initiation of ART (to evaluate whether the patient has been superinfected with a more resistant strain), and at each time an episode of virological failure occurs to assess whether the episode is associated with the development of resistance mutations (to inform on drug options available to choose from when composing next ART regimen), or not (if so, is the virological episode caused by non-disclosed interruption of ART?). When episodes of virological failure emerge, it is critical to harvest the sample prior to switching any of the components of ART, in order to optimize the chances of detecting drug resistance mutations.

What to do if resistance testing is not available for routine care?

Clinics are encouraged to sample plasma at indicated times and store them in a freezer, which allows for subsequent testing in cases where the clinical situation dictates it (reduces the resources required). The recommendations for use of ART in this document take into account the possibility of cross–resistance, so most PLHIV can be treated effectively without access to routine resistance testing.

Annex 4. HIV-1 protease and reverse transcriptase mutations for drug resistance surveillance

Programs that monitor local, national, and regional levels of transmitted HIV-1 drug resistance inform treatment guidelines and provide feedback on the success of HIV-1 treatment and prevention programmes. To accurately compare transmitted drug resistance rates across geographic regions and times, the World Health Organization has recommended the adoption of a consensus genotypic definition of transmitted HIV-1 drug resistance. The surveillance drug resistance mutation (SDRM) list is intended to provide a simple, unambiguous and stable measure of transmitted drug resistance in HIV-1. When used to assess resistance in a population-sampled set of HIV-1 sequences obtained from untreated individuals, the SDRM list provides an estimate of transmitted drug resistance in accordance with WHO guidelines. Mutations on the SDRM list have been selected for their suitability as indicators of transmitted resistance and conform to the following criteria: they are commonly recognized as causing or contributing to resistance; they are nonpolymorphic in untreated persons; and they are applicable to all HIV-1 subtypes.

Table 13. The World Health Organization 2009 list of mutations for surveillance of transmitted drug resistant HIV strains

NRTI		NNRTI		PI	
M41	L	L100	I	L23	I
K65	R	K101	E, P	L24	I
D67	N, G, E	K103	N, S	D30	N
T69	D, Ins	V106	M, A	V32	I
K70	R, E	V179	F	M46	I, L
L74	V, I	Y181	C, I, V	I47	V, A
V75	M, T, A, S	Y188	L, H, C	G48	V, M
F77	L	G190	A, S, E	I50	V, L
Y115	F	P225	H	F53	L, Y
F116	Y	M230	L	I54	V, L, M, A, T, S
Q151	M			G73	S, T, C, A
M184	V, I			L76	V
L210	W			V82	A, T, F, S, C, M, L
T215	Y, F, I, S, C, D, V, E			N83	D
K219	Q			I84	V, A, C
				I85	V
				N88	D, S
				L90	M

Source:(59)

Annex 5. Essential information about ARVs

TABLE 14.	ESSENTIAL ARV DRUG INFORMATION					
ARV	**Abbr.**	**Size**	**Dosage**	**Remarks**	**Major side-effects (cf. Table 11)**	**Resistance profile [a]**
NRTIs						
Abacavir	ABC	300 mg	300 mg tablet BID or 600 mg OD	No re-exposure if history of hypersensitivity reaction	Hypersensitivity reaction (fever, rash, and influenza-like symptoms such as GI and pulmonary symptoms)	65R/**N, 69Ins**, 74V/**I**, 115F, **151M,** 184V/I, TAM-1
Didanosine	ddI	250 mg 400 mg	PLHIV ≥60 kg: 400 mg capsule OD, PLHIV <60 kg: 250 mg capsule OD	Two hours after meal, dose reduction with TDF; not in combination with ribavarin	Peripheral polyneuropathy, pancreatitis, lactic acidosis	65R/**N**, 74V/**I, 69Ins, Q151M,** 184V/I, TAM-1
Emtricitabine	FTC	200 mg	200 mg capsule OD		Same as 3TC	65R, 184V/I
Lamivudine	3TC	300 mg 150 mg	300 mg tablet OD or 150 mg tablet BID		Rare diarrhoea	65R, 184V/I
Stavudine	d4T	30 mg	30 mg capsule BID	Not with ZDV, ddI	Peripheral neuropathy, lipodystrophy, elevation of ALT/AST	**TAM-1 and TAM-2, 75T/M, 69Ins, 151M** HSuscept: 184V/I
Tenofovir	TDF	300 mg	300 mg tablet OD	Dose reduction of ddI, not in combination with d4T; careful with renal insufficiency (dose reduction)	Renal insufficiency	**65R/N, 69Ins,** TAM-1, HSuscept: 74V, 184V/I
Zidovudine	ZDV	300 mg	300 mg tablet BID	Not with d4T or ribavirin; better susceptibility when 65R and 184V	Anaemia, GI, headache	41L **TAM-1 and TAM-2, 69Ins, 151M** HSuscept: 65R, 70E, 74V, 184V/I
ABC + 3TC	KVX	600 mg ABC, 300 mg 3TC	1tablet OD			
TDF + FTC	TVD	300 mg TDF, 200 mg FTC	1 tablet OD			
ZDV + 3TC	CBV	300 mg ZDV, 150 mg 3TC	1 tablet BID	Higher (historical) dose of ZDV (higher risk of side-effects)		

ARV	Abbr.	Size	Dosage	Remarks	Major side-effects (cf. Table 11)	Resistance profile [a]
ZDV + 3TC + ABC	TZV	300 mg ZDV, 150 mg 3TC, 300 mg ABC	1 tablet BID	Not once daily		
NNRTIs						
Efavirenz	EFV	600 mg	600 mg tablet OD	Start in the evening	Dizziness, sleeping disorders, psychiatric disorders (depression, risk of suicide)	98G, 100I, 101E/**P**, 103N/**S**, 106A/M, 108I, 179 D/E/F, 181C/I/V, 188L/H/C, 190A/S/**E**, 225H, 227C, 230L, 238T
Nevirapine	NVP	200 mg	200 mg tablet BID or 400 mg QD	First 14 days 200 mg OD, then 200 mg BID or 400 mg QD	Rash, liver enzyme elevation	98G, 100I, 101E/**P**, **103N/S**, **106A/M**, 108I, 179 D/E/F, **181C/I/V**, **188L/H/C**, **190A/S/E**, 227L/C, **230L**, **238T**
Etravirine	ETV	100 mg	200 mg BID	Tablets can be dissolved in water. Useful for subjects with difficulties in swallowing. Remains effective in the presence of K103N: useful for salvage therapy in some subjects with previous exposure to EFV or NVP.	Rash	Weighted classification of ETV RAMs (DUET trials): Weight 3: 181I/V; Weight 2.5: 101P, 100I, 181C, 230L; Weight 1.5: 138A, 106I, 190S, 179F; Weight 1: 90I, 179D/T, 101E/H, 98G, 190A. Weighted mutation score: 0-2 = Highest response; 2.5-3.5 = Intermediate response; ≥ 4 = response comparable to placebo.
PIs						
Atazanavir	ATV	150, 200, 300 mg capsules	300 mg OD plus 100 mg RTV OD or 400mg without RTV	With TDF ATV dose is 300/100mg	Bilirubin elevation (harmless), renal stones	24I, 33F, 46I/L, 47V, **48 V/M**, 50L, **53L,** 54V/L/M/T/A, **73S/T**, 82A/F/T/S, 84V/**A/C**, 88D/**S**, 90M HSuscept: 76V
Darunavir	DRV	75 mg 150 mg 300 mg 400 mg 600 mg	ART naïve or absence of PR mutations: 800 mg QD plus 100 mg RTV QD ART experienced: 600 mg tablet BID plus 100 mg RTV BID (experienced with PI mutations)	Use with RTV. QD dosing for naïve and BID dosing for treatment-experienced PLHIV; 900/100mg OD if limited PI resistance	Diarrhoea, hypertriglyceridemia, hypercholesterolemia	Weighted classification based on fold-change: FC>4= **50V**; FC 3-4=**54M, 76V, 84V**; FC 2-3= **32I, 33F, 47V, 74P**; FC<2= 11I, 54L, 89V. Interpretation: Diminished response to darunavir when 3 or more of these mutations are present. HSuscept: 50L

ARV	Abbr.	Size	Dosage	Remarks	Major side-effects (cf. Table 11)	Resistance profile [a]
Fosampren-avir	FPV	700 mg	700 mg tablet BID plus 100 mg capsule RTV BID	Dosage for treatment experienced PLHIV Use with RTV	Rash, headache, diarrhoea, dyslipidaemia	24I, 32I, 33F, **46I/L**, 47V/**A**, 50V, 54V/T/A/**L**/M, 73S/T, **76V**, 82A/F/T/S, 84V/**A/C**, **90M** HSuscept: 50L, 88S
Indinavir	IDV	400 mg	400 mg capsules BID plus 100 mg capsule RTV BID	Use with RTV	Kidney stones, dyslipidaemia, dry skin	24I, 32I, 36I, 46I/L, 53L, 54V/**T/A**/L/M, 73S/T, 76V, 82A/F/T/S, 84V/**A/C**, 88S, 90M HSuscept: 50L
Lopinavir/ ritonavir fixed combination	LPV/r	200 mg/50 mg	(200 mg/50 mg) x 2 BID or x 4 QD		Diarrhoea, meteorism, dyslipidaemia	24I, 32I, 33F, 46I/L, 47V/**A**, 48 V/M, **50V**, 54V/**T**/L,/**A/M**, 76V, 82A/F/T/**S**, 84V/**A/C**, 90M HSuscept: 50L
Nelfinavir	NFV	250 mg 625 mg	625 mg x 2 tablets BID or 250 mg x 5 tablets BID	With meal, reabsorption increases 270%; no booster with RTV	Diarrhoea, meteorism	**23I**, 24I, 30N, 36I36I36I33F, 46I/L, 47V, **48V/M**, **53L**, 54V/**T**/L/**A**/M, **73S**/T, 82A/F/T/S, 84V/**A/C**, 88D/S, 90M HSuscept: 50L
Ritonavir	RTV	100 mg	Only as a booster		Dyslipidaemia, liver enzyme elevation, diarrhoea	Not relevant
Saquinavir	SQV	500 mg	500 mg x 2 tablets BID plus 100 mg capsule RTV BID	New 500 mg tablets; was in 200 mg capsules until 2004. Use with RTV.	Diarrhoea and other GI symptoms, dyslipidaemia	48V/**M**, 53L, 54V/**T/A**/L/M, 73S/T, 82A/T, 84V/**A/C**, 88S, 90M HSuscept: 50L, 76V
Tipranavir	TPV	250 mg	250 mg x 2 capsules BID plus 100 mg x 2 capsules RTV BID	Dosage for treatment experienced PLHIV. Do not combine with other PIs. Use with RTV.	Dyslipidaemia (severe), liver enzyme elevation, diarrhoea	Weighted classification of TPV mutations (weight of each mutation): Major mutations: **47V** (+6), **54A/M/V** (+3), **58E** (+5), **74P** (+6), **82L/T** (+5), **83D** (+4); Minor mutations: 10V (+1), 36I (+2), 43T (+2), 46L (+1), 84V (+2) Increased response: 24I (-2), 50L/V (-4), 54L (-7), 76V (-2) Interpretation: Score ≤ 3: Susceptible; Score >3 and ≤ 10: Partially susceptible; Score >10: Resistant.

ARV	Abbr.	Size	Dosage	Remarks	Major side-effects (cf. Table 11)	Resistance profile [a]
Integrase inhibitors						
Raltegravir	RAL	400 mg	400 mg tablet BID, used with caution in patients with severe hepatic impairment	With or without food	Abnormal dreams, insomnia, dizziness, headache, vertigo, abdominal distension, abdominal pain, diarrhoea, flatulence, nausea, vomiting, rash, liver enzyme elevation	*Q148H/G7K/R7E, N155H, E157Q, E92Q, G140A/S, Y143C/H/R* **92Q**, **121Y**, 138A/K, **140G/S**, 143 **R/C**/H, 147G, **148H/R/K**, **155H**/S
Entry inhibitors						
Maraviroc	MRV	150 mg 300 mg	Depending on co-medication: 150 mg, 300 mg or 600 mg BID: If coadministered with potent CYP3A inhibitors (PIs except TPV, delavirdine, azoles, clarithromicin, nefazodone, telithromicine): 150 mg tablet BID Concomitant with potent CYP3A inducers (EFV, ETR, rifampin, carbamazepine, phenobarbital, phenytoin): 2 x 300 mg tablet BID	Maraviroc is a selective CCR5 antagonist; does not inhibit CXCR4-using viuses Requires prior tropism testing and should only be used in subjects with R5 virus.	Anaemia, insomnia, anorexia depression, abdominal pain, flatulence, nausea, rash, liver enzyme elevation Rare: potential for severe hepatotoxicity	*Virological failure to CCR5 antagonist-including therapy most often occurs due to the emergence of (pre-existing) X4 viruses rather than due to resistance to CCR5 antagonists.* *Resistance to small-molecule CCR5 antagonists may not result in the selection of stereotypical mutations. Rather, the selected mutations may lead to env-specific structural changes that allow gp120 to adapt to an inhibitor-bound conformation of CCR5. Most mutations described occur in the V3-loop stem, but the effect of mutations is context-dependent.*
Fusion Inhibitors						
Enfuvirtide	ENF	90 mg	90 mg/ml subcutaneous injection BID	No oral formulation	Skin reaction (itching, swelling, pain)	gp41: **36D/E**/V/S, 37V, **38E/A**/M/G, **40H**, 42T, **43D**/K/S, 44M, 45M

Modified from (304) and ttp://hivdb.stanford.edu/pages/download/

[a] Mutations in bold are associated with higher levels of phenotypic resistance or clinical evidence for reduced virological response. The remaining mutations are additionally selected during treatment failure or are accessory. There are two patterns of thymidine analogue resistance-associated mutations in reverse transcriptase: TAM1 (41L, 210W, 215Y) and TAM2 (67N, 70R and 219E/Q). “Hsuscept” refers to mutations conferring increased susceptibility to the drug.

Annex 6. Drug Interactions

Table 15. Contraindications

Co-medication	RTV as booster	ATV	DRV	FPV	LPV	SQV	EFV	NVP
Alfentanyl						●		
Alfusozin	●		●					
Amiodarone	●		●	●	●	●		
Amitriptyline						●		
Astemizole	●	●	●	●	●	●	●	
Atazanavir						●		
Bepridil	●	●	●	●		●	●	
Cisapride	●	●	●	●	●	●	●	
Clarithromycin						●		
Clorazepate	●							
Clozapine	●					●		
Dapsone						●		
Diazepam	●							
Diphemanil						●		
Disopyramide						●		
Dofetilide						●		
Encainide	●							
Ergot alkaloids	●	●	●	●	●	●	●	
Erythromycin						●		
Estazolam	●							
Fentanyl						●		
Flecainide	●			●		●		
Flurazepam	●							
Fusidic acid	●							
Halofantrine						●		
Haloperidol						●		
Hydroquinidine						●		
Ibutilide						●		
Imipramine						●		
Lidocaine			●			●		
Lopinavir			●			●		
Lovastatin	●		●		●	●		
Mesoridazine						●		
Methadone						●		
Mizolastine						●		
Midazolam							●	
Midazolam (oral)	●	●	●	●	●	●		
Pentamidine						●		
Pethidine	●							

Co-medication	RTV as booster	ATV	DRV	FPV	LPV	SQV	EFV	NVP
Phenothiazines						●		
Pimozide	●	●	●	●	●	●	●	
Piroxicam	●							
Propafenone	●			●		●		
Propoxyphene	●							
Quinidine	●	●	●	●		●		
Quinine						●		
Rifampicin		●	●	●		●		
Sertindole			●			●		
Sildenafil (as PDE5 inhibitor)						●		
Sildenafil (as Revatio for PAH)	●		●		●			
Simvastatin	●		●		●	●		
Sotalol						●		
Sparfloxacin						●		
St John's wort	●	●	●	●	●		●	●
Sultopride						●		
Tadalafil						●		
Terfenadine	●	●	●	●	●	●	●	
Thioridazine						●		
Trazodone						●		
Triazolam	●	●	●	●	●	●	●	
Vardenafil					●	●		
Vincamine (iv)						●		
Ziprasidone						●		

Source: Section 4.3 of the European SPCs; none listed for etravirine, maraviroc, raltegravir

Tables 16.1 to 16.6:	Interactions with ritonavir and ritonavir-boosted PIs (requiring dose modifications or monitoring taken from section 4.5 of European SPCs)

Table 16.1. Ritonavir (as a pharmacokinetic enhancer)

Co-medication	Plasma Concentration Effect		Recommendation
	Co-medication	RTV	
Antiretrovirals			
Indinavir, nelfinavir	↑		Appropriate doses have not been established.
Didanosine	↓		Separate dosing by 2.5h due to food requirements.
Maraviroc	↑		Decrease maraviroc dose to 150 mg twice daily.
Analagesics			
Buprenorphine	↑		No significant pharmacodynamics changes observed.
Fentanyl	↑		Monitor for therapeutic and adverse effects.
Methadone	↓		Consider increasing methadone dose based on clinical response.
Morphine	↓		
Anti- arrhythmics			
Digoxin	↑		Increased digoxin concentrations may lessen over time due to induction.
Anti-coagulants			
Warfarin	↓		Monitor INR.
Anti-convulsants			
Carbamazepine	↑		Monitor for therapeutic and adverse effects.
Divalproex, lamotrigine,	↓		Monitor for therapeutic and adverse effects.
Phenytoin	↓	↓	Monitor for therapeutic and adverse effects.
Anti-depressants			
Trazodone	↑		Start with lowest trazodone dose and monitor.
Anti-histamines			
Fexofenadine	↑		Increased fexofenadine concentrations may lessen over time due to induction.
Loratadine	↑		Monitor for therapeutic and adverse effects.
Anti-infectives			
Atovaquone	↓		Monitor therapeutic effects and atovaquone concentrations.
Rifabutin	↑		Consider a decrease in rifabutin dose.
Clarithromycin	↑ (↓ metabolite)		Do not coadminister clarithromycin doses >1 g/day. Decrease clarithromycin dose in renal impairment.
Erythromycin, itraconazole	↑		Monitor for therapeutic and adverse effects.
Ketoconazole	↑		Consider a decrease in ketoconazole dose.
Voriconazole	↓		Avoid unless clinically justified.

Co-medication	Plasma Concentration Effect		Recommendation
	Co-medication	RTV	
Anti-neoplastics			
Vincristine, vinblastine	↑		Potential for increased incidence of adverse reactions.
β2-agonists			
Salmeterol	↑		Coadministration not recommended.
Calcium Channel Blockers			
Amlodipine, diltiazem, nifedipine	↑		Monitor for therapeutic and adverse effects.
HMG Co-A Reductase Inhibitors			
Atorvastatin, rosuvastatin	↑		Start with lowest dose of atorvastatin or rosuvastatin.
Hormonal Contraceptives			
Ethinylestradiol	↓		Consider additional barrier methods of contraception.
Immunosuppressants			
Ciclosporin, tacrolimus, everolimus	↑		Monitor for therapeutic and adverse effects.
Phosphodiesterase (PDE5) Inhibitors			
Sildenafil, tadalafil, vardenafil	↑		Decrease dose of PDE5 inhibitor.
Sedatives/Hypnotics			
Alprazolam	↑ (RTV initiation)		Caution when starting RTV (first 10 days only).
Buspirone	↑		Monitor for therapeutic and adverse effects.
Midazolam (parenteral)	↑		Monitor closely. Decrease midazolam dose for multiple dosing.
Zolpidem	↑		Monitor for excessive sedative effects.
Smoking Cessation			
Bupropion	↓ (& metabolite)		Do not exceed recommended dose of bupropion.
Steroids			
Dexamethasone	↑		Monitor for therapeutic and adverse effects.
Fluticasone	↑		Avoid unless clinically justified.
Prednisolone	↑ (& metabolite)		Monitor for therapeutic and adverse effects.

Source: Norvir SPC, Abbott Laboratories Ltd, April 2010. (http://www.medicines.org.uk/emc, last accessed 24/01/2011)

Table 16.2. Atazanavir

Co-medication	Plasma Concentration Effect		Recommendation
	Co-medication	ATV	
Antiretrovirals			
Didanosine (buffered tablets)		↓	Administer 2 h apart due to food requirements.
Didanosine (enteric coated, with food)	↓		Decreased didanosine concentrations due to food.
Efavirenz		↓	Coadministration not recommended.
Indinavir			Coadministration not recommended due to indirect unconjugated hyperbilirubinaemia.
Nevirapine	↑	↓	Coadministration not recommended.
Ritonavir		↑	RTV 100 mg once daily used as booster.
Tenofovir	↑	↓	Monitor for tenofovir toxicities.
Analagesics			
Buprenorphine	↑ (& metabolite)		Monitor for sedation and cognitive effects. Consider a decrease in buprenorphine dose.
Anti-arrhythmics			
Amiodarone, lidocaine (systemic)	↑		Use with caution. Monitor anti-arrhythmic concentration.
Anticoagulant			
Warfarin	?		Monitor INR.
Anti-infectives			
Clarithromycin	↑ (↓ metabolite)	↑	Use with caution.
Ketoconazole, itraconazole	↑		Use with caution. Azole doses >200 mg/day not recommended.
Rifabutin	↑ (& metabolite)		Decrease rifabutin dose to 150 mg 3 times a week. Monitor for rifabutin toxicities.
Voriconazole	↓	↓ RTV	Not recommended unless clinically justified.
Anti-neoplastics			
Irinotecan	↑		Monitor closely for irinotecan toxicities.
Calcium Channel Blockers			
Diltiazem	↑ (& metabolite)		Decrease diltiazem dose by 50% and titrate as required. Monitor ECG.
Verapamil	↑		Use with caution.
Gastrointestinal Agents			
Antacids		↓	Administer ATV 2 h before or 1 h after antacids.
Famotidine (and other H2 receptor antagonists)		↓	Do not exceed a dose equivalent to famotidine 20 mg twice daily unless clinically justified. Avoid in PLHIV taking ATV and TDF.
Omeprazole		↓	Coadministration not recommended.
HMG Co-A Reductase Inhibitors			
Atorvastatin	↑		Use with caution.
Simvastatin, lovastatin	↑		Coadministration not recommended.
Hormonal Contraceptives			
Ethinylestradiol	↓		Use contraceptives with at least 30 µg ethinylestradiol.

Co-medication	Plasma Concentration Effect		Recommendation
	Co-medication	ATV	
Norgestimate	↑		No data with other progestogens. Alternative reliable method of contraception recommended.
Immunosuppressants			
Ciclosporin, tacrolimus, sirolimus	↑		Monitor immunosuppressant concentrations.
Phosphodiesterase (PDE5) Inhibitors			
Sildenafil	↑		Monitor for sildenafil toxicities and warn patient about possible side effects.
Sedatives/Hypnotics			
Midazolam (parenteral)	↑		Monitor closely. Decrease midazolam dose for multiple dosing.
Steroids			
Fluticasone	↑		Not recommended unless clinically justified.

Source: Reyataz SPC, Bristol-Myers Squibb Pharmaceuticals Ltd, September 2010 (http://www.medicines.org.uk/ems, accessed 24/01/2011)

Table 16.3. Darunavir

Co-medication	Plasma Concentration Effect		Recommendation
	Co-medication	DRV	
Antiretrovirals			
Didanosine	↓		Administer 1 h before or 2 h after DRV due to food requirements.
Efavirenz	↑	↓	Monitor for efavirenz toxicities.
Indinavir	↑	↑	Consider decreasing indinavir to 600 mg twice daily in cases of intolerance.
Maraviroc	↑		Decrease maraviroc dose to 150 mg twice daily.
Saquinavir	↓	↓	Coadministration not recommended.
Tenofovir	↑	↑	Monitor renal function.
Analagesics			
Buprenorphine	↓ (↑ metabolite)		Monitor for opiate toxicities.
Methadone	↓		Monitor. An increased methadone dose may be required with long term administration.
Anti-arrhythmics			
Digoxin	↑		Start with lowest digoxin dose and titrate.
Anti-coagulants			
Warfarin	?		Monitor INR.
Anti-convulsants			
Carbamazepine	↑	↓	Monitor for carbamazepine toxicities. Consider a decrease in carbamazepine dose.
Phenobarbital, phenytoin		↓	DRV should not be used in combination with these anticonvulsants.
Anti-depressants			
Paroxetine, sertraline	↓		Dose titrate based on clinical response.
Anti-gout			
Colchicine	↑		Decrease colchicine dose or suspend treatment. Do not use in hepatic/renal impairment.
Anti-hypertensives			
Tadalafil (for PAH)	↑		Coadministration not recommended.
Anti-infectives			
Clarithromycin	↑	↓	Use with caution.
Clotrimazole		↑	Use with caution and monitor.
Itraconazole, ketoconazole	↑	↑	Use with caution and monitor. Do not exceed azole daily dose of 200 mg.
Rifabutin	↑	↑	Decrease rifabutin dose by 75%. Monitor for rifabutin toxicities.
Voriconazole	↓		Do not coadminister unless clinically justified.
β2-agonists			
Salmeterol	↑		Coadministration not recommended.
Calcium Channel Blockers			
Felodipine, nicardipine, nifedipine	↑		Monitor for therapeutic and adverse effects.
Endothelin Receptor Antagonists			
Bosentan	↑		Monitor tolerability of bosentan.

Co-medication	Plasma Concentration Effect		Recommendation
	Co-medication	DRV	
HMG Co-A Reductase Inhibitors			
Atorvastatin, pravastatin	↑		Start with lowest dose of statin and titrate.
Hormonal Contraceptives			
Ethinylestradiol	↓		Alternative or additional barrier methods of contraception are recommended.
Norethisterone (Norethindrone)	↓		Alternative or additional barrier methods of contraception are recommended.
Immunosuppressants			
Ciclosporin, tacrolimus, sirolimus	↑		Monitor immunosuppressant concentrations.
Phosphodiesterase (PDE5) Inhibitors			
Sildenafil, tadalafil, vardenafil	↑		Use with caution and decrease PDE5 inhibitor dose.
Sedatives/Hypnotics			
Midazolam (parenteral)	↑		Monitor closely. Decrease midazolam dose for multiple dosing.
Steroids			
Dexamethasone (systemic)		↓	Use with caution.
Fluticasone, budesonide	↑		Not recommended unless clinically justified.

Source: Prezista SPC, Janssen-Cilag Ltd, November 2010 (http://www.medicines.org.uk/emc, accessed 24/01/2011)

Table 16.4. Fosamprenavir

Co-medication	Plasma Concentration Effect		Recommendation
	Co-medication	FPV	
Antiretrovirals			
Etravirine		↑	A decrease in fosamprenavir dose may be needed.
Indinavir, nelfinavir, saquinavir			No dose recommendations can be given.
Lopinavir	↑	↓	Coadministration is not recommended.
Analagesics			
Methadone	↓		Monitor for withdrawal symptoms.
Anti-arrhythmics			
Lidocaine (systemic)	↑		Coadministration not recommended.
Anti-coagulants			
Warfarin	?		Monitor INR.
Anti-convulsants			
Carbamazepine, phenobarbital		↓	Use with caution.
Phenytoin	↓		Monitor phenytoin concentrations.
Anti-depressants			
Desipramine, nortriptyline	↑		Monitor for therapeutic and adverse effects.
Paroxetine	↓		Dose titrate based on clinical response.
Anti-infectives			
Clarithromycin, erythromycin	↑		Use with caution.
Halofantrine	↑		Coadministration not recommended.
Itraconazole, ketoconazole	↑		Azole doses >200 mg/day not recommended.
Rifabutin	↓ (↑ metabolite)		Decrease rifabutin dose by 75%. Further dose decreases may be necessary.
HMG Co-A Reductase Inhibitors			
Atorvastatin	↑		Monitor. Do not exceed atorvastatin 20 mg/day.
Lovastatin, simvastatin	↑		Coadministration not recommended.
Hormonal Contraceptives			
Ethinylestradiol	↓	↑ RTV	Alternative, non-hormonal methods of contraception recommended.
Norethisterone	↓	↑ RTV	Alternative, non-hormonal methods of contraception recommended.
Immunosuppressants			
Ciclosporin, tacrolimus, sirolimus	↑		Monitor immunosuppressant concentrations.
Phosphodiesterase (PDE5) Inhibitors			
Sildenafil, vardenafil	↑		Coadministration not recommended.
Sedatives/Hypnotics			
Midazolam (parenteral)	↑		Monitor closely. Decrease midazolam dose for multiple dosing.
Steroids			
Fluticasone	↑		Not recommended unless clinically justified.

Source: Telzir SPC, ViiV Health care United Kingdom Ltd, August 2010 (http://www.medicines.org.uk/emc, accessed 24/01/2011)

Table 16.5. Lopinavir

Co-medication	Plasma Concentration Effect		Recommendation
	Co-medication	LPV	
Antiretrovirals			
Abacavir, zidovudine	↓		Clinical significance unknown.
Efavirenz		↓	Increase Kaletra dose to 500/125 mg twice daily. Do not administer with **once daily** Kaletra.
Nevirapine		↓	Increase Kaletra dose to 500/125 mg twice daily. Do not administer with **once daily** Kaletra.
Fosamprenavir	↓		Coadministration not recommended.
Indinavir	↑		Appropriate doses not established.
Nelfinavir		↓	Appropriate doses not established.
Tipranavir		↓	Coadministration not recommended.
Tenofovir	↑		Monitor for tenofovir toxicities.
Analagesics			
Fentanyl	↑		Monitor for fentanyl toxicities.
Methadone	↓		Monitor methadone concentrations.
Anti-arrhythmics			
Bepridil, digoxin, lidocaine (systemic), quinidine	↑		Use with caution. Monitor anti-arrhythmic concentrations.
Anti-coagulants			
Warfarin	?		Monitor INR.
Anti-convulsants			
Carbamazepine, phenobarbital	↑	↓	Use with caution. Monitor anticonvulsant concentrations. Consider increasing Kaletra dose. Do not administer with **once daily** Kaletra.
Phenytoin	↓	↓	Use with caution. Monitor phenytoin concentrations. Consider an increase in Kaletra dose. Do not administer with **once daily** Kaletra.
Anti-depressants			
Trazodone	↑		Use with caution. Consider trazodone dose decrease.
Anti-infectives			
Clarithromycin	↑		Consider clarithromycin dose decrease in renal impairment.
Ketoconazole, itraconazole	↑		Azole doses >200 mg/day not recommended.
Rifabutin	↑ (& metabolite)		Decrease rifabutin dose by 75%. Further dose decreases may be necessary.
Rifampicin		↓	Not recommended unless clinically justified. If unavoidable consider LPV/r 400/400 mg twice daily with close monitoring.
Voriconazole	↓		Avoid coadministration unless clinically justified.

Co-medication	Plasma Concentration Effect		Recommendation
	Co-medication	LPV	
Anti-neoplastics			
Dasatinib, nilotinib, vincristine, vinblastine	↑		Monitor tolerance of anti-neoplastic drugs.
Calcium Channel Blockers			
Felodipine, nicardipine, nifedipine	↑		Monitor therapeutic and adverse effects.
HMG Co-A Reductase Inhibitors			
Atorvastatin	↑		Coadministration not recommended.
Rosuvastatin	↑		Use with caution. Consider rosuvastatin dose decrease.
Hormonal Contraceptives			
Ethinylestradiol	↓		Use additional methods of contraception.
Immunosuppressants			
Ciclosporin, tacrolimus, sirolimus	↑		Monitor immunosuppressant concentrations.
Phosphodiesterase (PDE5) Inhibitors			
Sildenafil, tadalafil	↑		Use with caution and decrease PDE5 inhibitor dose.
Sedatives/Hypnotics			
Midazolam (parenteral)	↑		Monitor closely. Decrease midazolam dose for multiple dosing.
Smoking Cessation			
Bupropion	↓ (& metabolite)		Not recommended unless clinically justified. If unavoidable, do not exceed recommended dose and monitor bupropion efficacy closely.
Steroids			
Dexamethasone		↓	Monitor antiviral efficacy.
Fluticasone	↑		Not recommended unless clinically justified.

Source: Kaletra SPC, Abbott Laboratories Ltd, August 2010 (http://www.medicines.org.uk/emc, accessed 24/01/2011)

Table 16.6.	Saquinavir		
Co-medication	**Plasma Concentration Effect**		**Recommendation**
	Co-medication	**SQV**	
Antiretrovirals			
Indinavir	↑		Increased IDV may result in nephrolithiasis.
Nelfinavir	↓	↑	Combination not recommended.
Tipranavir		↓	Coadministration not recommended.
Anti-arrhythmics			
Digoxin	↑		Use with caution. Monitor and consider decreasing digoxin dose.
Anti-coagulants			
Warfarin	?		Monitor INR.
Anti-infectives			
Ketoconazole	↑		Ketoconazole doses >200 mg/day not recommended.
Rifabutin	↑	↓	Decrease rifabutin dose to 150 mg twice weekly.
Calcium Channel Blockers			
Felodipine, nicardipine, nifedipine, diltiazem, nimodipine, verapamil, amlodipine, nisoldipine, isradipine	↑		Use with caution and monitor.
Gastrointestinal Agents			
Omeprazole (and other proton pump inhibitors)		↑	Combination not recommended.
HMG Co-A Reductase Inhibitors			
Atorvastatin	↑		Use lowest atorvastatin dose and monitor.
Pravastatin, fluvastatin	?		If no alternatives, use with careful monitoring.
Hormonal Contraceptives			
Ethinylestradiol	↓		Use alternative or additional contraceptive methods.
Immunosuppressants			
Ciclosporin, tacrolimus, sirolimus	↑		Monitor immunosuppressant concentrations.
Sedatives/Hypnotics			
Alprazolam, clorazepate, diazepam, flurazepam	↑		Monitor for sedative effects. A decreased dose of benzodiazepines may be needed.
Midazolam (parenteral)	↑		Monitor closely. Decrease midazolam dose for multiple dosing.
Steroids			
Fluticasone	↑		Not recommended unless clinically justified.

Source: Invirase SPC, Roche Products Ltd, January 2011 (http://www.medicines.org.uk/emc, accessed 24/01/2011)

Tables 17.1 to 17.3:	Interactions with NNRTIs (requiring dose modifications or monitoring; taken from section 4.5 of European SPCs)

Table 17.1. Efavirenz

Co-medication	Plasma Concentration Effect		Recommendation
	Co-medication	EFV	
Antiretrovirals			
Atazanavir/ritonavir	↓		Coadministration not recommended. If unavoidable, increase dosing of ATV and RTV.
Darunavir/ritonavir	↓	↑	Use with caution.
Indinavir (unboosted)	↓		Clinical significance of decreased indinavir concentrations not established.
Lopinavir/ritonavir	↓		Increase lopinavir dose to 500/125 or 533/133 mg twice daily.
Maraviroc	↓		Increase maraviroc dose to 600 mg twice daily.
Analagesics			
Buprenorphine	↓		No signs of withdrawal observed.
Methadone	↓		Monitor for withdrawal and increase methadone dose as required.
Anti-coagulants			
Warfarin	?		Dose adjustment of warfarin may be needed.
Anti-convulsants			
Carbamazepine	↓	↓	Consider alternative anticonvulsant or monitor carbamazepine concentrations.
Phenytoin, phenobarbital	↑		Monitor anticonvulsant concentrations.
Anti-depressants			
Sertraline	↓	↑	Sertraline dose increases should be guided by clinical response.
Anti-infectives			
Clarithromycin	↓ (↑ metabolite)	↑	Clinical significance of changes in clarithromycin concentrations not established. Consider alternatives.
Itraconazole	↓ (& metabolite)		Consider alternative antifungal agents.
Posaconazole	↓		Avoid coadministration unless clinically justified.
Rifabutin	↓	↓	Increase daily rifabutin dose by 50% or double if given 2-3 times weekly.
Rifampicin		↓	Consider increasing efavirenz dose to 800 mg.
Voriconazole	↓	↑	Increase voriconazole dose to 400 mg twice daily and decrease efavirenz dose by 50%.
Calcium Channel Blockers			
Diltiazem	↓ (& metabolite)	↑	Adjust diltiazem dose based on clinical response.
Verapamil, felodipine, nifedipine, nicardipine	↓		Dose adjustments of calcium channel blockers should be guided by clinical response.

Co-medication	Plasma Concentration Effect		Recommendation
	Co-medication	EFV	
HMG Co-A Reductase Inhibitors			
Atorvastatin, pravastatin, simvastatin	↓		Dose adjustment of statin may be required.
Hormonal Contraceptives			
Depo medroxyprogesterone acetate	(limited data)		Use additional barrier method of contraception.
Etonogestrel implant	↓		Use additional barrier method of contraception.
Ethinylestradiol	↓		Use additional barrier method of contraception.
Norgestimate	↓ metabolites		Use additional barrier method of contraception.
Immunosuppressants			
Ciclosporin, tacrolimus, sirolimus	↓		Monitor immunosuppressant concentrations until at steady state.

Source: Sustiva SPC, Bristol-Myers Squibb Pharmaceuticals Ltd, November 2010 (http://www.medicines.org.uk/emc, accessed 24/01/2011)

Table 17.2. Etravirine

Co-medication	Plasma Concentration Effect		Recommendation
	Co-medication	ETR	
Antiretrovirals			
Efavirenz, nevirapine		↓	Coadministration not recommended.
Fosamprenavir	↑		A decrease in fosamprenavir dose may be required.
Indinavir (unboosted)	↓		Coadministration not recommended.
Nelfinavir	↑		Coadministration not recommended.
Tipranavir	↑	↓	Coadministration not recommended.
Anti-arrhythmics			
Amiodarone, bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine	↓		Use with caution. Monitor anti-arrhythmic concentrations.
Digoxin	↑		Monitor digoxin concentrations.
Anti-coagulants			
Warfarin	↑		Monitor INR.
Anti-convulsants			
Carbamazepine, phenytoin, phenobarbital		↓	Coadministration not recommended.
Anti-infectives			
Clarithromycin	↓ (↑ metabolite)	↑	Consider alternatives for the treatment of MAC.
Rifabutin (+ PI)	↑	↓	Use with caution.
Rifampicin, rifapentine		↓	Coadministration not recommended.
Herbals			
St John's wort		↓	Coadministration not recommended.
HMG Co-A Reductase Inhibitors			
Atorvastatin	↓ (↑metabolite)		Adjust atorvastatin dose based on clinical response.
Fluvastatin	↑		Dose adjustment of fluvastatin may be needed.
Lovastatin, simvastatin	↓		Dose adjustment of statins may be needed.
Rosuvastatin	?		Dose adjustment of rosuvastatin may be needed.
Immunosuppressants			
Ciclosporin, tacrolimus, sirolimus	↓		Use with caution.
Phosphodiesterase (PDE5) Inhibitors			
Sildenafil, tadalafil, vardenafil	↓		Dose adjustment of PDE5 inhibitor may be required.
Sedatives/Hypnotics			
Diazepam	↑		Consider alternatives to diazepam.
Steroids			
Dexamethasone (systemic)		↓	Use with caution. Consider alternatives, especially for chronic use.

Source: Intelence SPC, Janssen-Cilag Ltd, April 2010 (http://www.medicines.org.uk/emc, accessed 24/01/2011)

Table 17.3.	Nevirapine		
Co-medication	**Plasma Concentration Effect**		**Recommendation**
	Co-medication	**NVP**	
Antiretrovirals			
Efavirenz	↓		Coadministration not recommended.
Atazanavir	↓	↑	Coadministration not recommended.
Fosamprenavir (unboosted)	↓	↑	Coadministration not recommended.
Lopinavir	↓		Increase lopinavir to 500/125 (or 533/133) mg twice daily.
Analagesics			
Methadone	↓		Monitor for withdrawal and increase methadone dose as required.
Anti-coagulants			
Warfarin	?		Monitor INR.
Anti-infectives			
Clarithromycin	↓ (↑ metabolite)	↑	Consider alternatives. Monitor for hepatic abnormalities.
Fluconazole		↑	Use with caution. Monitor for NVP toxicities.
Itraconazole	↓		Consider increasing itraconazole dose.
Ketoconazole	↓	↑	Coadministration not recommended.
Rifabutin	↑ (& metabolite)		Use with caution due to high intersubject variability.
Rifampicin		↓	Coadministration not recommended.
Hormonal Contraceptives			
Ethinylestradiol	↓		Use additional barrier method of contraception.
Norethindrone	↓		Use additional barrier method of contraception.

Source: Viramune SPC, Boehringer Ingelheim Ltd, August 2010 (http://www.medicines.org.uk/emc, accessed 24/01/2011)

Tables 18.1 to 18.2:	Interactions with maraviroc or raltegravir (requiring dose modifications or monitoring; taken from section 4.5 of European SPCs)

Table 18.1. Maraviroc

Co-medication	Plasma Concentration Effect		Recommendation
	Co-medication	MRV	
Antiretrovirals			
Efavirenz		↓	Increase maraviroc dose to 600 mg twice daily.
Atazanavir, lopinavir, saquinavir, darunavir, nelfinavir, indinavir		↑	Decrease maraviroc dose to 150 mg twice daily.
Anti-infectives			
Clarithromycin, telithromycin		↑	Decrease maraviroc dose to 150 mg twice daily.
Ketoconazole, itraconazole		↑	Decrease maraviroc dose to 150 mg twice daily.
Rifabutin (+ PI)		↑	Decrease maraviroc dose to 150 mg twice daily (except with TPV/r or FPV/r).
Rifampicin		↓	Increase maraviroc dose to 600 mg twice daily (in the absence of a potent CYP3A4 inhibitor).
Herbals			
St John's wort		↓	Coadministration not recommended.

Source: Celsentri SPC, ViiV Health care United Kingdom Ltd, June 2010 (http://www.medicines.org.uk/emc, accessed 24/01/2011)

Table 18.2. Raltegravir

Co-medication	Plasma Concentration Effect		Recommendation
	Co-medication	RAL	
Anti-infectives			
Rifampicin		↓	If coadministration is unavoidable, consider doubling raltegravir dose.
Gastrointestinal Agents			
Omeprazole		↑	Do not coadminister raltegravir with acid reducing agents unless clinically justified.

Source: Isentress SPC, Merck Sharp & Dohme Ltd, September 2010 (http://www.medicines.org.uk/emc, accessed 24/01/2011)

Annex 7. Tools for adherence monitoring

Self-reporting is a good adherence marker, but it is not perfect. It seems to overestimate ART adherence more than other methods *(304)*. To be effective, the patient must be willing to disclose problems, particularly face to face. This method may be important in reinforcing the central role of PLHIV in managing their own adherence, as opposed to provider-controlled methods.

Provider estimates of adherence have been demonstrated to be poor *(305)* and are not advisable.

Drug-level monitoring is not widely available as there is no commercial test. It is not a method for routine control of adherence, and can only reveal a snapshot of the time the sample is taken *(306)*. In case of low plasma drug levels, adherence has to be discussed. Laboratory markers like serum bilirubin level or mean corpuscular volume of erythrocytes might show adherence to ATV or ZDV and to a lesser extent d4T, and bilirubin levels are associated with ATV use.

Medication Event Monitoring System (MEMS) is frequently used in research settings. An electronic device fitted to pill boxes records the removal of the cap. It is associated with predictable virological response to ART *(306)*. It is not possible with blister packs.

Pharmacy drug pick up or prescription records. This involves assessing whether the amount of drug the patient has picked up over a period is sufficient to cover that period, taking into account pick up patterns. This is an objective measure that may be a good measure of long term adherence but is not sensitive to short term changes. Like many other methods, could be inaccurate in some situations, e.g. if the patient picks up the drug regularly but does not take it *(217,307,308)*.

Pill identification test (PIT) is a novel method that correlates with validated self-reporting measures *(309)*. PLHIV are invited to distinguish the pills of their regimen from a display of ARVs, including two "twin pills", which are similar but not identical to their own.

The use of **surrogate markers** is reliable but too late when poor adherence is revealed. Individuals with virological failure on a PI-containing regimen had low PI blood levels, low adherence levels by pill count and an absence of genotypic resistance to PIs, suggesting their treatment failure had been caused by low adherence *(310,311)*. Providers have to be careful with interpretation of these markers, however, because of other possible reasons for low drug levels *(204)*.

Annex 8. List of antiretroviral drugs[3]

Table 19. Antiretroviral drug list

International Non-proprietary Name (INN)	Proprietary Name	Pharmaceutical Company
NRTIs		
Abacavir (ABC)	Epzicom: United States, Kivexa: United Kingdom (lamivudine/abacavir) Trizivir: Europe, United Kingdom, United States (zidovudine/lamivudine/abacavir) Ziagen: United Kingdom, United States	Viiv
	Abavir	Genixpharma
	Virol Virol LZ (abacavir/lamivudine/zidovudine)	Ranbaxy
Didanosine (ddI)	Videx, Videx EC	Bristol-Myers Squibb
	Dinex EC Odivir Kit (didanosine/lamivudine/efavirenz)	Cipla
	Aviro-Z Virosine Viro-Z	Ranbaxy
	Divir	Thai Government
Emtricitabine (FTC)	ATRIPLA (efavirenz/emtricitabine/tenofovir)	Bristol-Myers Squibb and Gilead Sciences
	Emtriva Truvada (tenovovir/emtricitabine)	Gilead Sciences
Lamivudine (3TC)	Combivir: United Kingdom, United States (lamivudine/zidovudine) Epivir: United Kingdom, United States, Zeffix: United Kingdom Epzicom: United States, Kivexa: United Kingdom (lamivudine/abacavir) Trizivir: Europe, United States (zidovudine/lamivudine/abacavir)	Viiv
	Lamivox Stavex-L (lamivudine/stavudine) Stavex-LN (lamivudine/nevirapine/stavudine) Zidovex-L (lamivudine/zidovudine) Zidovex-LN (lamivudine/nevirapine/zidovudine)	Aurobindo
	Duovir (lamivudine/zidovudine) Duovir-N (lamivudine/nevirapine/zidovudine) Lamivir Odivir Kit (didanosine/lamivudine/efavirenz) Triomune (lamivudine/nevirapine/stavudine)	Cipla

[3] This list is a compilation of those ARVs that are widely used, and should not be construed to be exhaustive. It was accurate as of 9th February 2011. ***Disclaimer:*** The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned.

International Non-proprietary Name (INN)	Proprietary Name	Pharmaceutical Company
Lamivudine (3TC)	Heptavir Lamistar 30, Lamistar 40 (lamivudine/stavudine) Nevilast (lamivudine/nevirapine/stavudine) Zidolam (lamivudine/zidovudine)	Genixpharma
	Virolam Virocomb (lamivudine/zidovudine) Virolans (lamivudine/nevirapine/stavudine) Virolis (lamivudine/stavudine) Virol LZ, Abac-ALZ (abacavir/lamivudine/zidovudine)	Ranbaxy
Stavudine (d4T)	Zerit, Zerit XR	Bristol-Myers Squibb
	Stavex Stavex-L (lamivudine/stavudine) Stavex-LN (lamivudine/nevirapine/stavudine)	Aurobindo
	Stavir Lamivir-S (lamivudine/stavudine) Triomune (lamivudine/nevirapine/stavudine)	Cipla
	Lamistar (lamivudine/stavudine) Nevilast (lamivudine/nevirapine/stavudine) Stag	Genixpharma
	Stavir	GPO (Thailand)
	Avostav Triviro-LNS (lamivudine/nevirapine/stavudine) Virolans (lamivudine/nevirapine/stavudine) Virolis, Coviro (lamivudine/stavudine) Virostav	Ranbaxy
Tenofovir (TDF)	Truvada (tenofovir/emtricitabine) Viread (tenofovir)	Gilead Sciences
	ATRIPLA (efavirenz/emtricitabine/tenofovir)	Bristol-Myers Squibb
Triple nucleoside (TRZ)	Trizivir: Europe, United States (zidovudine/lamivudine/abacavir)	Viiv
Zidovudine (ZDV or AZT)	Combivir: United Kingdom, United States (lamivudine/zidovudine) Retrovir: United Kingdom, United States Trizivir: Europe, United States (zidovudine/lamivudine/abacavir)	Viiv
	Zidovex	Aurobindo
	Zidovir Duovir (lamivudine/zidovudine)	Cipla
	Zido-H (zidovudine)	Genixpharma
	Antivir	GPO (Thailand)
	Aviro-Z Virocomb (lamivudine/zidovudine) Virol LZ (abacavir/lamivudine/zidovudine) Viro-Z	Ranbaxy

International Non-proprietary Name (INN)	Proprietary Name	Pharmaceutical Company
NNRTIs		
Efavirenz (EFV)	Sustiva: Europe, United Kingdom, Stocrin: Australia, Europe, Latin America, South Africa ATRIPLA (efavirenz/emtricitabine/tenofovir)	Bristol-Myers Squibb
	Viranz	Aurobindo
	Efavir	Cipla
	Estiva	Genixpharma
	Efferven	Ranbaxy
aNevirapine (NVP)	Viramune	Boehringer Ingelheim
	Nevirex Stavex LN (lamivudine/nevirapine/stavudine)	Aurobindo
	Duovir-N (lamivudine/nevirapine/zidovudine) Nevimune Triomune (lamivudine/nevirapine/stavudine)	Cipla
	Nevilast (lamivudine/nevirapine/stavudine)	Genixpharma
	GPOVir	GPO (Thailand)
	Nevipan Triviro LNS (lamivudine/nevirapine/stavudine) Virolans (lamivudine/nevirapine/stavudine) Zidovex-LN (lamivudine/nevirapine/zidovudine)	Ranbaxy
Etravirine /ETV)	Intelence	Janssen-Cilag, Johnson & Johnson
Integrase Inhibitors		
Raltegravir (RAL)	Isentress	MSD
Entry inhibitors		
Maraviroc (MRV)	Celsentri	Viiv
Fusion Inhibitors		
Enfuvirtide (T-20)	Fuzeon: United Kingdom, United States	Roche Pharmaceuticals & Trimeris, Inc.
Protease Inhibitors		
Amprenavir (APV)	Agenerase: United Kingdom, United States	Viiv
Atazanavir (ATV)	Reyataz	Bristol-Myers Squibb
Darunavir (DRV)	Prezista	Janssen-Cilag, Johnson & Johnson
Fosamprenavir (FPV)	Lexiva: US, Telzir: United Kingdom	Viiv and Vertex
Indinavir (IDV)	Crixivan	Merck & Co.
	Indivex	Aurobindo
	Indivir	Cipla and Genixpharma
	Virodin	Ranbaxy
Lopinavir/ritonavir combination (LPV/r)	Kaletra Aluvia	Abbott Laboratories

International Non-proprietary Name (INN)	Proprietary Name	Pharmaceutical Company
Nelfinavir (NFV)	Viracept	Pfizer, Inc., Roche Pharmaceuticals
	Nelvex	Aurobindo
	Nelvir	Cipla
	Nelfin	Genixpharma
	Nefavir	Ranbaxy
Ritonavir (RTV)	Norvir	Abbott Laboratories
	Ritovir	Hetero/Genix
Saquinavir (SQV)	Fortovase: Europe, United Kingdom, United States Invirase: United Kingdom, United States	Roche Pharmaceuticals

Annex 9. Glossary

Adherence is patient ability to take ARV drugs as prescribed at specific time. High adherence is defined as taking over 95% of doses; suboptimal adherence is anything under this level. Some drugs (e.g. those with a long half-life) are likely to be more tolerant of suboptimal adherence than others.

Backbone is the part of ARV treatment, usually consisting of two NRTIs used in combination with an NNRTI or a PI or an integrase inhibitor. "Optimized backbone" means an adjusted combination of probable working NRTIs based on results of resistance testing.

Genetic barrier is a description of the number of mutations needed for the virus to be resistant to a drug. Resistance with 1 mutation means a low genetic barrier; resistance with 10 mutations means a very high genetic barrier, though this characterization is subject to change. Concept of genetic barrier also applies to a regimen as a whole.

Major mutations are the changes in viral RNA that encode for resistance to particular ART drugs or ART classes.

Minor mutations work in combination and can lead to resistance or counteract the effects from other major or minor mutations on virus susceptibility to antiviral drugs and its fitness to replicate.

A **point mutation** is one change in the RNA code resulting in resistance to a drug or class of drugs. For example, in ART treatment mutation 103 means a resistance to all NNRTIs, resulting from changes in virus at specific point (103).

Drug resistance occurs when mutations in viral genetic material occur (leading to a change in amino acid and hence in a virus protein). Most changes lead to the death of the virus; other changes are viable. Drug resistance is when a mutation leads to a virus that has an increased capacity to replicate in the presence of a drug because it can survive the mechanisms of ART. In most cases, resistance leads to poorer viral fitness, meaning a slower HIV replication rate in the absence of drug than virus without the mutation.

Thymidine analogue mutations (TAMs) are usually a result of ZDV treatment.

Annex 10. Beyond the horizon

Research on how to compose ART to improve adherence, efficacy and tolerability, and how ART should be used best strategically continues. The following are some of the concepts of which we can expect some level of clarification in the coming years.

When to initiate ART

Provision of ART reduces the risk of opportunistic infections and directly HIV-induced diseases, and reduces the risk of MTCT. It is also plausible that ART slows the progression of liver fibrosis associated with chronic HBV and HCV infection. The current set of guidelines suggests how to use ART to exploit these benefits. It is currently postulated that ART may also reduce the risk of other co-morbidities such as cardiovascular disease, chronic obstructive pulmonary disease, non-AIDS cancers, as well as liver or kidney disease not directly attributed to viral hepatitis coinfection and HIV itself. There are ongoing randomized trials aiming at clarifying whether the benefits reach beyond those we know of. If so, this will have major implications for when to initiate ART.

There are also ongoing discussions on whether more widespread usage of ART (beyond the criteria cited in the present version of the guidelines) would lead to reduction in new HIV infection incidence. It is evident that the infectiousness of the individual PLHIV is reduced on ART, but will a strategy of more widespread use of it (possible in PLHIV not currently needing it) lead to substantive reductions in the spread of the virus, thereby curtailing the epidemic? Exciting research is underway to elucidate this important public health question.

Many PLHIV enter care late in the course of their HIV infection, and die because ART has been started too late. These deaths are avoidable if health systems could improve their ability to diagnose and enter PLHIV into care earlier in the course of their infection. Strategic research to resolve this major public health problem is urgently required.

How to compose ART

It is likely that the choices for first-line ART will be diversified in the years to come. Use of regimens without NRTIs and possibly reducing the number of drugs to combine are currently under investigation. Newer drugs are also being tested, including second-generation NNRTIs and integrase inhibitors. Once the effectiveness and tolerability of these alternative ways of combining ART have been clarified, additional research will be required to clarify the strategic question of which sequence of composing ART provides the most durable benefit.

The concept of fixed-dose combinations and QD dosing has prevailed as optimizing the chances of adherence. There are multiple ways to make fixed-dose combinations, and we will likely see a substantive expansion of various types of drugs being composed in the years to come.

A (functional) cure for HIV

This is a concept that is the focus of continued intense research. However, a safe and reliable approach to eradication of HIV from the body of a person already infected is difficult to envision. Therefore, the concept of "functional cure" has evolved, i.e. no eradication of the infection but rather maintaining health without use of ART. Research is attempting to identify interventions to achieve this. In the mean time, it is achievable to maintain a normal (or close to a normal) lifespan if ART is initiated relatively early in the course of HIV infection, and is fully effective and well-tolerated for the remainder of the person's life. Many PLHIV have already achieved this state, and we hope that these guidelines will assist in making this vision true for many more.

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